# Dietary Calcium and Magnesium, Calcium/magnesium Ratio, and Mortality: Results from the Shanghai Women's and Men's Health Studies

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2012-002111 |
| Article Type: | Research |
| Date Submitted by the Author: | 13-Sep-2012 |
| Complete List of Authors: | Dai, Qi; Vanderbilt School of Medicine, Department of Medicine<br>Shu, Xiao-Ou; Vanderbilt School of Medicine, Department of Medicine<br>Deng, Xinqing; Vanderbilt School of Medicine, Department of Medicine<br>Xiang, Yong-bing; Shanghai Cancer Institute, Department of Epidemiology<br>Li, Honglan; Shanghai Cancer Institute, Department of Epidemiology<br>Yang, Gong; Vanderbilt School of Medicine, Department of Medicine<br>Shrubsole, Martha; Vanderbilt School of Medicine, Department of Medicine<br>Ji, Butian; National Institutes of Health, 3Division of Cancer Epidemiology and Genetics<br>Cai, Hui; Vanderbilt School of Medicine, Department of Medicine<br>Chow, Wong-Ho<br>Gao, Yu-Tang; Shanghai Cancer Institute, Department of Epidemiology<br>Zheng, Wei; Vanderbilt School of Medicine, Department of Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Nutrition and metabolism |
| Keywords: | Public health < INFECTIOUS DISEASES, EPIDEMIOLOGY, NUTRITION & DIETETICS |
| | |

**Original Research Article**

# Dietary Calcium and Magnesium, Calcium/magnesium Ratio, and Mortality: Results from the Shanghai Women's and Men's Health Studies

Qi Dai[1], Xiao-Ou Shu[1], Xinqing Deng[1], Yong-bing Xiang[2], Honglan Li[2], Gong Yang[1], Martha J Shrubsole[1], Butian Ji[3], Hui Cai [1], Wong-Ho Chow[3,4], Yu-Tang Gao[2], Wei Zheng[1]

[1]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt School of Medicine, 37203

[2]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China;

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892

[4]Department of Epidemiology, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX

Correspondence to: Dr. Qi Dai, Vanderbilt Epidemiology Center, Institute for Medicine & Public Health, Sixth Floor, Suite 600, 2525 West End Avenue, Nashville, TN 37203-1738

Phone: 615-936-0707, Fax: 615-936-8290, E-mail: qi.dai@vanderbilt.edu

**Running Title:** calcium/magnesium ratio and mortality

**Key words:** Magnesium, calcium, ratio, mortality, cancer and cardiovascular diseases

## ABSTRACT

**Objectives** Magnesium (Mg) and calcium (Ca) antagonize each other in (re)absorption, inflammation and many other physiologic activities. Based on mathematical estimation, the absorbed number of Ca or Mg depends on the dietary ratio of Ca to Mg intake. We tested the hypotheses that dietary Ca/Mg ratio modify the effects of Ca and Mg on mortality due to gastrointestinal tract cancer, and perhaps, mortality due to diseases occurring in other organs or systems.

**Design** We conducted analyses using data from two large population-based cohorts (Shanghai Women's and Men's Health Studies) conducted in China with over 130,000 participants.

**Results** In this Chinese population with a low Ca/Mg intake ratio, intakes of Mg greater than US RDA levels (≥320 mg/day among women and ≥420 mg/day among men) were related to increased risks of total mortality for both women and men. Consistent with our hypothesis, Ca/Mg intake ratio significantly modified the associations of intakes of Ca and Mg with mortality risk whereas no significant interactions between Ca and Mg in relation to outcome were found. The associations differed by gender. Among men with Ca/Mg ratio > median (1.7), increased intakes of Ca and Mg were associated with reduced risks of total mortality, and mortality due to coronary heart diseases. In the same group, intake of Ca was associated with a reduced risk of mortality due to cancer. Among women with Ca/Mg ratio ≤ 1.7, intake of Mg was associated with increased risks of total mortality, and mortality due to cardiovascular diseases (including coronary heart disease and stroke) and colorectal cancer.

**Conclusions** These results, if confirmed, may help to understand the optimal balance between Ca and Mg in the etiology and prevention of these common diseases and reduction in mortality.

## Article summary

*Article focus*

- Modifying effects of Ca/Mg intake ratio on the associations between intakes of Ca and Mg with disease mortality
- The effect of high Mg intake on disease mortality differs in populations with a very low Ca/Mg intake ratio from those (i.e. Western populations) with a high ratio
- Modifiying effects of sex on the associations between intakes of Ca and Mg with disease mortality

*Key messages*

- Significant modifying effects of combined Ca/Mg intake ratio, but not Mg or Ca intake alone, on the associations between intakes of Ca and Mg, respectively, with risk of total mortality and coronary heart diseases and possibly cancer
- In contrast to studies conducted in the US, high intake of Mg was related to an increased risk of total mortality among both men and women a similar Mg intake level but a low Ca/Mg intake ratio.
- Sex significantly modified the associations between intakes of Ca and Mg with disease mortality

*Strengths and limitations of this study*

- Population-based prospective design with large sample sizes
- High rates for baseline participation and follow-up
- A unique population with a low Ca/Mg intake ratio
- Adjustment for many potential confounding factors
- Similar results in sensitivity analysis by excluding those who used Ca or multivitamin supplements
- Caution for the generalization of findings to populations with a high Ca/Mg ratio
- The Ca and Mg contents of drinking water not included

- Small sample size in the analyses by cancer subtype, particularly among men

## INTRODUCTION

Magnesium (Mg) and calcium (Ca) belong to the same family in the periodic table and share the same homeostatic regulating system[1] involving Ca sensing receptor (CaSR) and (re)absorption[2]. Meanwhile, Mg and Ca antagonize each other in many physiologic activities [2-8]. It was not until recently that Mg was thought to share ion transporters with Ca in (re)absorption[9]. Mg ion transporters identified in recent years (e.g. TRPM7) also have affinity for Ca[9]. In the intestine, Ca and Mg may directly or indirectly compete for intestinal absorption [2]. A low concentration of Ca and a high concentration of Mg (thus, a low Ca:Mg) in the lumen activates mucosal transport of Mg [2]. A high Ca intake reduces absorption rates for both Mg and Ca in humans [2;4].

Colon lumen concentrations for $Ca^{2+}$ and $Mg^{2+}$ are monitored by the same receptor, the CASR [1]. If the body needs to absorb a total of ten molecules of Ca and Mg, and the diet contains five molecules of Ca and five of Mg, all five Ca and five Mg molecules are absorbed. If the diet consists of forty five Ca and five Mg, nine Ca and one Mg are absorbed. Thus, if the total absorbed number of Ca and Mg is relatively constant, the absorption number for Ca is dependent upon $Ca*(1/(Ca+Mg)) =(Ca/Mg +1)^{-1}$, in which solely the Ca/Mg ratio varies. It is also true for Mg. Thus, we postulated that the dietary ratio of Ca to Mg modifies the effects of Ca and Mg intakes on cancer carcinogenesis [10;11]. In a study conducted in the US, we found high intake of total Ca or Mg may only be related to a reduced risk of colorectal adenoma when the Ca/Mg ratio was below 2.78 [10]. In a randomized clinical trial conducted in the US, Ca treatment only significantly reduced colorectal adenoma recurrence risk when the baseline dietary Ca/Mg ratio was under 2.63 and this effect modification by the Ca/Mg ratio cannot solely be attributed to the baseline dietary intake in either Ca or Mg[11]. In another study, high serum Ca/Mg ratio was

associated with an increased risk of high-grade prostate cancer after controlling for serum Ca and Mg[12]. However, all these studies have been conducted in high Ca/Mg ratio populations.

Many studies conducted in Western countries have linked low intake of Mg to insulin resistance[13] and systemic inflammation[14] and, thus, risk of diseases common in Western countries, such as metabolic syndrome [15], type II diabetes[16-18], coronary heart disease[19-21] and cancer[10;22-24]. East Asians have much lower incidence and mortality rates of coronary heart disease and colorectal cancer, but much higher rates of stroke compared to their counterparts in US. However, mean intake of Mg [25;26] in East Asia[10] is equivalent to the US population [27] whereas the Ca/Mg intake ratio is almost halved in the Chinese population compared to the US population [25;28]. Thus, it is possible that the differential Ca/Mg intake ratio may contribute, in part, to the different incidence and mortality rates of these common diseases[10].

The low Ca/Mg ratio range (below median) in the Western populations is overlapping with the high ratio range in the Chinese population (above median) (See **Figure 1**). Thus, we further hypothesize that in Chinese populations, intakes of Mg and Ca may only be related to a reduced risk of mortality due to colorectal cancer and, perhaps, other common diseases when dietary Ca/Mg ratio is above median (1.7). Conversely, previous studies indicate that high Mg intake led to a negative Ca balance when Ca intake was low (i.e. low Ca/Mg ratio) [29]. Thus, high Mg intake may have a detrimental effect when Ca/Mg ratio is very low (below 1.7). We tested these hypotheses in two population-based cohorts conducted in China with over 130,000 participants.

## METHODS

***SWHS and SMHS:*** The Shanghai Women's Health Study (SWHS) and the Shanghai Men Health Study (SMHS) are two population-based, prospective cohort studies conducted in urban Shanghai, China. In both studies similar designs which were described in detail elsewhere, were utilized [30;31]. In brief, during 1996 and 2000, the SWHS recruited 74, 942 female participants aged 40 to 70 years from seven urban communities representative of urban Shanghai with a participation rate of 92.7% while from 2002 to 2006, the SMHS enrolled 61, 500 men aged 40 to 74 years from the same seven communities with a participation rate of 74.1%. Certified interviewers elicited information on demographic characteristics, medical history, anthropometrics, usual dietary habits, physical activities, and other lifestyle factors. At least two measurements were conducted for weight, height, and circumferences of the waist and hips at the in-person interview. The study was approved by all relevant institutional review boards. The study was approved by all relevant institutional review boards in China (Shanghai Cancer Institute) and the United States (Vanderbilt University).

***Cohort follow-up and outcome ascertainment:*** The SWHS and SMHS participants have been followed-up by biennial home visit as well as annual record linkage to the population-based Shanghai Cancer Registry and Vital Statistics Registry. In the current study, the primary outcomes included deaths from all causes, deaths from cardiovascular diseases (including coronary heart diseases and stroke) and deaths from cancers occurring between the baseline recruitment and the most recent follow-up and/or annual vital status linkage. The follow-up rate for vital status in both cohorts was >99.9% complete[32;33]. In this analysis, in order to allow for the delay in records processing, the date of the last follow-up was set as Dec, 31, 2009 for study

participants, 6 months before the most recent record linkage (June 30, 2010). The underlying causes for deaths were determined based primarily on death certificates from Shanghai Vital Statistics Registry which are coded using the *International Classification of Diseases, Ninth Revision* (ICD-9). Studies have been conducted to validate cause-of-death statistics in urban China, which also includes urban Shanghai, and data on death certificates have shown reasonable accuracy for major causes of deaths including cancer and cardiovascular diseases [34].

***Exposure Measurement and Covariates:*** Usual dietary intakes were assessed through in-person interviews using validated food-frequency questionnaires (FFQs) (11,12) in SMHS[35] and SWHS[36]. Nutrient intakes (i.e. dietary Ca and Mg), were derived from FFQs using the Chinese food composition tables (Institute of Nutrition and Food Safety, China CDC, 2004). A wide array of covariates assessed at the baseline survey and FFQs were compared by levels of exposure (intake levels of Ca and Mg) as potential confounding factors (Table 1).

***Statistical Analysis*** To be consistent with SMHS, we excluded from the analysis 1,579 subjects with a history of cancer at baseline from the SWHS. We also excluded 126 subjects in SWHS and 70 in SMHS with unreasonably high or low energy intake (<500 or >3,500 kcal/day for women; <500 or >4,200 kcal/day for men), and 8 subjects in SWHS and 14 in SMHS who moved away from Shanghai immediately after the baseline survey. As a result, a total of 73,232 for SWHS and 61,414 for SMHS were included in the final analyses.

We estimated the main associations using hazard ratio (HR) in Cox proportional hazard regression models[37], using age at entry and age at death or age at censor as a time-scale[38]. To be

consistent with previous cohort studies which evaluated the association of Ca and Mg with disease risks[10;22;23], we have adjusted for the following potential confounding factors: age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng (yes, no), alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium and zinc. Log-transformation was conducted for continuous variables.

Since intake level of Mg in our study population is comparable to the studies conducted in Western countries, we have used the US's Mg Recommended Daily Allowance (RDA) for women (320 mg/day), which is very close to the 66th percentile of Mg intake in our study population (321 mg/day), as the upper cutpoint. In contrast, very few study participants had a Ca intake level above the current US Daily Reference Intake (DRI) for Ca (1000 mg/day). Thus, we have used 600 mg/day, a previous Ca DRI for Chinese (Institute of Nutrition and Food Safety and Chinese Institute for Preventive Medicine, 1991), as the upper cutpoint. We utilized the medians of Mg and Ca for the remaining participants as the lower cutpoint. Since the intake levels of Mg and Ca in men were higher than women, we have added one cutpoint (i.e. US RDA for Mg in men (420 mg/day)) for Mg and one cutpoint (i.e. the current DRI for Ca in Chinese adults (800 mg/day)) for Ca in the analysis for men.

Separate analyses were conducted for SWHS (women) and SMHS (men). The first model was adjusted for age and other confounding factors except for Ca and Mg. In the second model, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of

Ca or Mg, respectively. Stratified analyses by medians of Ca/Mg ratio[10;11], Ca or Mg intake[11] were conducted. In the stratified analyses, the full-adjusted (second) model was used. In addition, we have conducted sensitivity analyses by excluding those who took Ca supplement or multivitamin. Tests for trend across exposure categories were performed by entering the categorical variables as a continuous variable in the model. *P* values of < 0.05 (2-sided probability) were interpreted as being statistically significant. Statistical analyses were conducted by using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

## RESULTS

Selected demographic characteristics and potentially confounding factors were compared by intake levels of Ca and Mg separately for SWHS and SMHS as shown in **Table 1**. Proportions of participants with high educational achievement, female alcohol drinkers, tea drinkers, users of Ca, multivitamin and ginseng supplements, and those who were physically active and consumed high levels of (energy- and age-adjusted) saturated fatty acids, fiber, phosphorus, retinol, vitamin E, folate, sodium, potassium, zinc and Mg or Ca increased with increasing intakes of Ca and Mg. The proportion of participants that smoked, male alcohol drinkers, and those who were not married decreased with increasing intakes of Ca and Mg.

In the pooled analysis of SMHS and SWHS, we found that sex significantly modified the associations between intakes of Ca and Mg with risk of total mortality (*P* for interactions < 0.01) and mortality due to cardiovascular diseases (*P* for interactions < 0.01). Sex also appeared to

modify the associations of Ca and Mg with cancer (*P* for interactions were 0.125 for Mg and 0.280 for Ca, respectively). Thus, separate analyses were conducted for SWHS and SMHS. Presented in **Table 2** are the associations of dietary intakes of Ca and Mg with risk of total mortality, mortality due to cardiovascular diseases and cancer in SWHS. After adjusting for potentially confounding factors (model 1) and additionally controlling for Ca or Mg, respectively (model 2), we found that among women, high intake of Mg was significantly associated with 35-50% increased risks of mortality due to cardiovascular diseases, particularly stroke. Furthermore, Ca/Mg ratio modified the associations between intake of Mg and risk of total mortality (*P* for interaction, 0.07) and mortality due to coronary heart diseases (*P* for interaction, 0.02) in model 2. Among those with Ca/Mg ratio ≤ 1.7, intake of Mg was significantly associated with 24% -66% increased risks of total mortality and mortality due to cardiovascular diseases (including stroke and coronary heart disease), and an 120% increased risk of colorectal cancer (P for trend, 0.05). On the other hand, among those with Ca/Mg intake ratio > 1.7, intake of Mg was related to a decreased risk of lung cancer (P for trend, 0.01); and intake of Ca was associated with significantly reduced risk of cancer (P for trend, 0.02) including lung cancer (P for trend, 0.01) and colorectal cancer (P for trend, 0.05), but was related to an increased risk of gastric cancer. In the sensitivity analyses conducted by excluding those who used Ca or multivitamin supplements, similar results were observed (Data not shown).

**Table 3** shows the associations between dietary intakes of Ca and Mg and risk of total mortality, mortality due to cardiovascular diseases and cancer in SMHS using the same cutpoints as those for women in SWHS (Table 2). Among men, high intake of Ca (≥600 mg/day) were related to reduced risks of total mortality and mortality due to cardiovascular diseases and, possibly, cancer

while intake of Mg (≥320 mg/day) was possibly related to a reduced risk of death due to coronary heart diseases. In the stratified analysis (model 2), we found the associations between intakes of Ca and Mg and risk of total mortality and cardiovascular diseases were modified by Ca/Mg ratio with the *p* for interactions ranging from 0.01 to 0.07. Among participants with Ca/Mg intake ratio > 1.7, risks of total mortality, and mortality due to coronary heart disease and cancer were significantly reduced with increasing intakes of Ca and Mg. These associations were statistically significant except for the non-significant inverse association between Mg and cancer. In contrast, among those with Ca/Mg ratio ≤ 1.7, intakes of Ca and Mg were not significantly related to risks. The sample size became very sparse in the analysis for subtype cancers due to a shorter follow-up time for SMHS (men) compared to SWHS (women) and none of the associations was significant (Data not shown). Analyses limited to those who did not use Ca or multivitamin supplements generated similar results (Data not shown).

Men had higher intake levels of Ca and Mg than women. In **Table 4**, we repeated the analyses presented in Table 3, but added one cutpoint (420 mg/day, RDA for US men) for Mg and one cutpoint (800 mg/day, the current DRI for Chinese) for Ca. We found that highest intake of Mg (≥420 mg/day) was significantly associated with increased risks of total mortality and mortality due to cancer. We also found Ca intake levels between 600-800 mg/day, but not higher than 800 mg/day, may be associated with reduced risks of total mortality and mortality due to cardiovascular diseases and cancer. It is worth noting at borderline significance, high Ca intake was associated with a reduced risk of death due to colorectal cancer while Mg intake was associated with an increased risk of gastric cancer mortality, particularly among those with

Ca/Mg ratio ≤1.7 (*P* for interaction, 0.05). Analyses limited to those who did not use Ca or multivitamin supplements generated similar results (Data not shown).

We have also conducted stratified analyses to examine whether Ca intake directly interacted with Mg intake in relation to risk of total mortality, mortality due to cardiovascular diseases (coronary heart diseases and stroke) and cancer. For both men and women, we found Mg intake was associated with a significantly increased risk of total mortality among those with Ca intake equal to or below median, but was associated with a significantly reduced risk among those with Ca intake above the median (**Table 5**). Among men Ca intake was associated with a reduced risk of total mortality when Mg intake was above the median while Ca intake was not significantly associated with the risk among those with Mg intake below the median. Similar findings were observed for women although none of the association was statistically significant. These findings indicate a pattern for interactions between Ca and Mg. However, Ca-Mg interactions were not statistically significant for total mortality (Table 5), and mortality due to cardiovascular diseases (coronary heart diseases and stoke) and cancer and its subtypes in both SWHS and SMHS (Data not shown).

## DISCUSSION

### Statement of principal findings

In contrast to studies conducted in the US with a high Ca/Mg ratio which generally found inverse associations, we found in Chinese populations with a low Ca/Mg intake ratio that high intake of Mg (≥320 mg/day for women and ≥420 mg/day for men) was related to an increased risk of total

mortality among both men and women, mortality due to cardiovascular diseases among women and mortality due to cancer among men. Furthermore, we found that Ca/Mg ratio significantly modified the associations between intakes of Ca and Mg with risk of total mortality and coronary heart diseases and possibly cancer whereas we did not identify any significant interactions between Ca and Mg in relation to these outcomes. Among those with Ca/Mg ratios above the median, intakes of Ca and Mg were associated with reduced risks of total mortality, and mortality due to coronary heart diseases for both men and women, and cancer for men while Mg intake was associated with a decreased risk of cancer mortality for women. Conversely, among those with Ca/Mg ratio equal to or below the median, intake of Mg was associated with increased risks of total mortality and mortality due to cardiovascular diseases for men and women as well as colorectal cancer for women and possibly gastric cancer for men.

**Hypothesis and overall biological mechanism**

Ionized Ca has a central role in cellular signaling [39], controlling numerous cellular processes [40], while ionized Mg is essential in over 300 biological activities[8]. Ca and Mg have similar chemical properties and share the same homeostatic regulating system including gut absorption and kidney reabsorption to maintain a normal balance of Ca and Mg[1]. Furthermore, the changes in blood or colon lumen concentrations for $Ca^{2+}$ and $Mg^{2+}$ are monitored by the same receptor, the calcium-sensing receptor (CASR) [1]. Once the Ca or Mg concentration is high, CASR could respond to it even if the concentration of Mg or Ca, respectively, is low, resulting in the simultaneous depression of the (re)absorption process for both Ca and Mg[2;4]. Thus, in clinics, hypomagnesemia is commonly linked to secondary hypocalciuria[41]. Previous studies also showed that changes in the dietary Ca/Mg balance affected systemic inflammation responses in

animal models [3;14]. In addition to inflammation, $Mg^{2+}$ and $Ca^{2+}$ potentially antagonize each other in many other physiologic activities, such as oxidative stress[42] and insulin resistance [18;43], DNA repair, cell differentiation and proliferation, apoptosis, and angiogenesis [3;6;44], which may also be involved in development of cancer, cardiovascular diseases and many other diseases. As we mentioned in the introduction, if the total absorbed number of Ca and Mg molecules is relatively constant, the absorbed numbers of Ca and Mg are dependent on Ca/Mg ratio in the gut. Therefore, the Ca/Mg ratio to which gut epithelial cells are directly exposed may modify absorption of Ca and Mg and other activities in gut[10;11].

**Comparison with previous studies**

*Possible explanations on findings with colorectal cancer:* In 2007, we reported from a study conducted in US that Mg intake from dietary source was only related to a non-significantly reduced risk of colorectal adenoma while total Mg intake from both dietary and supplemental source was associated with a significantly reduced risk [10]. The inverse associations with both total intakes of Ca or Mg may primarily appear among those with Ca/Mg ratio was below 2.78 [10]. Similar to our finding, in a very recent case-control study conducted in Netherlands, Wark et al. found dietary Mg only (not including Mg from supplementation) was marginally significantly related to a reduced risk of colorectal adenoma[45]. In our 2007 report, we found the p for interaction between total Mg and total Ca/Mg ratio was 0.10[10] whereas p for interaction was 0.65 between dietary Mg and dietary Ca/Mg ratio. Interestingly, the study conducted by Wark et al. also did not find a significant interaction between dietary Mg and dietary Ca/Mg ratio (p for interaction=0.86)[45]. It is possible that misclassification in the analyses due to only using Ca and Mg from dietary source may bias the result to the null. In a recent paper based on the analysis of

a large clinical trial, Ca treatment reduced risk of colorectal adenoma recurrence only among those with baseline dietary Ca/Mg ratio less than or equal to 2.63[10;11]. Moreover, the effect of Ca treatment did not significantly differ by baseline intake of Ca or Mg alone[11;46]. Zhang et al found in the Nurses' Health Study, the interaction between total Ca and Mg intakes (p for interaction, 0.17) was also not statistically significant in relation to risk of colorectal cancer incidence[47]. Consistent with these published findings, we found in the current study that the associations between Ca or Mg with total mortality and mortality due to cardiovascular diseases and cancer were not significantly modified by Mg or Ca, respectively, but many of these associations were significantly modified by Ca/Mg ratio.

*Overall interpretations for findings on diseases other than colorectal cancer:* In a recent study, we found high serum Ca/Mg ratio was statistically associated with an increased risk of high-grade prostate cancer even after adjusting for both serum Ca and Mg[12], indicating that the balance between Ca and Mg may affect risk or pathogenesis of diseases other than colorectal cancer or adenoma. In addition to competition for absorption, a previous study found that Mg supplementation increased urinary Ca excretion if intake of Ca was <800 mg/day[29], suggesting that Mg may suppress Ca reabsorption when Ca/Mg intake ratio is very low. It is possible that the Ca and Mg statuses in the body and specific organs or tissues could be indirectly modified by the dietary Ca/Mg ratio through affecting both absorption and reabsorption processes [29;48]. As a result, it is not surprising that we found the dietary Ca/Mg ratio also modified the effects of Ca and Mg on risk of diseases occurring in organs which do not directly expose to dietary Ca and Mg. However, it is conceivable through the homeostasis regulation by (re)absorption, the Ca/Mg ratio in the gut differs from that in circulation and other systems. Thus, the modification effects

of dietary Ca/Mg ratio may become weaker on diseases occurring in organs other than the digestive tract. For example, among women with Ca/Mg ratio ≤ 1.7, high intake of Mg was associated with a 24% of increased risk of total mortality and 66% increased of coronary heart disease death compared to 120% increased risk for colorectal cancer death. Among women with Ca/Mg >1.7, intake of Ca has the strongest inverse association with gastrointestinal cancer.

*Comparison with studies on association of Mg with CVD:* The associations between Mg intake with risk of stroke [49;50] and coronary heart disease [49;51]incidence and death have not been entirely consistent in previous prospective studies. Two meta-analyses found that Mg intake was related to a significantly reduced risk of stroke [49;50]. However, the inverse association was weak and only existed with ischemic stroke, but not hemorrhagic stroke [50]. Also, a previous meta-analysis found Mg intake was non-significantly inversely associated with coronary heart disease[49]. No study has examined the possible effect modifications by the Ca/Mg ratio. A very recent report from the JACC study conducted in Japan, a population also with a low Ca/Mg ratio, found that dietary intake of Mg was significantly related to reduced risks of mortality due to hemorrhagic stroke in men and cardiovascular diseases in women [51]. However, after adjusting for intakes of Ca and potassium, all these inverse associations not only disappeared, but further became positive associations, which were significant for total stroke in women with an HR (95% CI) of 1.81(1.12-2.94) for the highest quintile intake vs. the lowest (*P* for trend, 0.015) and of borderline significance for ischemic stroke in women (*P* for trend, 0.081). Thus, these findings from the study conducted in a Japanese population are consistent with what we found in Chinese populations. Furthermore, previous cohort studies have relatively consistently found high dietary intake of Mg was associated with a reduced risk of metabolic syndrome [15] and type II diabetes [16-18] and insulin resistance [13] in Western populations. However, clinical trials using

different high doses of Mg supplementations led to inconsistent results on glycaemic control among diabetes patients[52]. The null effect in many of these trials could be due to a high dose of Mg supplementation resulting in a very low Ca/Mg ratio (<1.7). Future studies are needed to confirm this possibility.

*Comparison with studies on association of Ca with CVD:* Similar to Mg, previous cohort studies have also provided inconsistent results on the associations between Ca intake and supplemental use of Ca and risk of cardiovascular diseases[53;54]. Meta-analysis of these studies showed a non-significant result with either coronary heart disease or stroke [53]. No study has examined whether the Ca/Mg ratio modifies the association between Ca intake and risk of cardiovascular disease incidence or death. A recent study conducted among a population with a high intake level of Mg found intake of Ca, but not Mg, to be associated with a reduced risk of total mortality and, likely, mortality due to cardiovascular diseases [54]. In joint analysis, intake of Ca was significantly related to a reduced risk of total mortality only when intake of Mg was under 480 mg/day. It is very important to mention that this study was conducted in a population located in the northern latitude where sunlight is very limited for vitamin D synthesis during spring to autumn [55]. Furthermore, the investigators excluded those who took dietary supplements including vitamin D supplements from the study. As a result, the average intake level of vitamin D was as low as 6.5 µg / day. Thus, it is expected in a population at high risk of vitamin D deficiency that Ca intake would be related to a reduced risk of total mortality even at a very high level, particularly among those with relatively low intake of Mg (no competition from Mg). In contrast, although still controversial, recent findings from reanalysis of the Women's Health Initiative study and meta-analysis of secondary clinical trials data conducted among populations

with high Ca/Mg ratio suggest that high Ca supplementation with or without vitamin D may modestly increase the risk of cardiovascular events, especially myocardial infarction[56;57]. Also, we found Ca intake levels between 600-800 mg/day, but not higher than 800 mg/day, may be associated with reduced risks of total mortality and mortality due to cardiovascular diseases and cancer. Our finding is supported by the results from both the Nurses' Health Study and the Health Professionals Follow-up Study. In these two studies, the furthest reduction in risk of colorectal cancer associated with intake of Ca was achieved by intakes of 700-800 mg/day, but no additional reduction in risk was observed at higher intakes of Ca [58].

In additional analysis in the JACC, the reduction in risk of mortality due to coronary heart disease was only significant among those with both high intakes of Ca and Mg compared to those with both low intakes[51]. This finding indicates that high Ca plus high Mg, not high Ca or Mg alone was not significantly associated with a reduced risk. The Ca/Mg ratio for people who had both high Ca and high Mg intakes or those with both low Ca and low Mg intakes is in the middle range (i.e. smaller than those with a high Ca and a low Mg intake, but greater than those with a low Ca and a high Mg intake). Among those with a Ca/Mg ratio in the middle, high intakes of Ca and Mg had a reduced risk compared to those with low intakes of Ca and Mg. Thus, this joint association between Ca with Mg found in the JACC is in general consistent with the modifying effects by Ca/Mg ratio observed in the current study. We have also replicated this joint analysis in the current study and found a similar finding among men, but not women. Also, in the current study, we found many significant interactions between Ca/Mg ratio with Ca or Mg, but zero significant interactions between Ca and Mg intakes in relation to disease mortality,

suggesting Ca/Mg ratio has a stronger modifying effect than Ca or Mg alone. The fact is also consistent with that predicted mathematically.

*Possible interpretations on the sex modification:* In the current study, we found Mg intake (≥320 mg/day) among women and a higher dose among men (i.e. Mg intake ≥420 mg/day) was related to an increased risk of total mortality. Furthermore, we found the associations between intakes of Ca and Mg and risk of total mortality and mortality due to cardiovascular diseases significantly differed by sex. These findings are biologically meaningful because of the effects of estrogen on Mg and Ca metabolism [59]. For example, estrogen shifted Mg from circulation (serum) into cells and, thus, lower Mg intake was required for young women than young men to keep positive magnesium balance[59]. Seelig proposed that the increase of the Ca/Mg intake ratio from 2.0 in 1920s to over 3.0 in the US contributed to a sharp rise in incidence of cardiovascular diseases in men, but not women[59] and this ratio is continuously rising in recent years[60]. Some previous cohort studies conducted in populations with high Ca/Mg ratio have also provided some support. For example, the Atherosclerosis Risk in Communities study found an inverse association between Mg intake and serum Mg and risk of coronary heart disease in men, but not in women and *P* for interaction was 0.07 for serum Mg with sex [61]. Although a meta-analysis association for cohort studies was not significant, all studies conducted among men had an RR/HR under 1.00 for the association between Mg intake and risk of coronary heart disease while only two studies conducted among women had an RR/HR above 1.00[49]. Mg was weakly, but significantly associated with a reduced risk of stroke in a very recent meta-analysis[50]. However, Health Professionals' Follow-up Study found an inverse association between Mg intake and risk of stroke, particularly among men with hypertension, whereas Mg intake was not

related to risk among Nurses' Health Study[49]. Further studies are necessary to understand the potential sex modifications.

*Interesting preliminary observations on gastric cancer and stroke:* One interesting, but preliminary, observation in the current study is that Mg intake may be associated with an increased risk of deaths due to stroke and gastric cancer (among men). Previous studies found that compared to the world average, the Chinese population had a much lower incidence and mortality rate of coronary diseases, but a much higher incidence and mortality rate of stroke; [62] and China is also among the regions with the highest rate of gastric cancer, particularly among men[63]. It is possible that the low Ca/Mg ratio in Chinese populations may partially contribute to the higher risks. However, further studies are necessary to explore this possibility.

**Strengths and weaknesses**

The strengths include a population-based prospective design, large sample size, and high rates for baseline participation and follow-up, which minimize potential differential recall bias or selection bias. The current study has been conducted in a population with a low Ca/Mg intake ratio. Thus, caution should be used to generalize our findings to populations with a high Ca/Mg ratio before further studies have been conducted to examine whether Ca/Mg ratio or Mg and Ca modifies the associations of Ca and Mg intakes with risk of non-gastrointestinal diseases [10;11] in populations with a high Ca/Mg ratio. We have adjusted for many potential confounding factors, including Ca supplement and multivitamin use, and also found similar results in sensitivity analysis by excluding those who used Ca or multivitamin supplements. However, the Ca and Mg contents of drinking water could not be calculated. This may lead to non-differential

misclassification of Ca and Mg intake, which usually biases associations toward the null. Finally, sample size became smaller in the analyses by cancer subtype, particularly among men. Thus, some of the null associations in subtype analysis could be due to a small sample.

**Conclusion and clinical and public health implications**

In the current study conducted in populations with lower Ca/Mg ratios, we found that when the Ca/Mg ratio was above 1.7, high intake of Ca was related to a reduced risk of colorectal cancer death and the reduction in risk was the strongest among all the associations between Ca and disease mortality. Conversely, among those with Ca/Mg ratio less than or equal to 1.7, high intake of Mg was related to a significantly increased risk of mortality due to colorectal cancer in women. Collectively, the findings from the current study as well as some previous studies conducted in populations with high Ca/Mg ratios [10;11] indicate that a Ca/Mg ratio between 1.70 and 2.63 may be required for intakes of Ca and Mg to be protective against colorectal cancer. In addition to colorectal cancer, the potential modifications by the dietary Ca/Mg ratio and sex may provide possible explanations for the inconsistencies on the associations between intake of Ca and Mg with risk of coronary heart diseases[49;53;54], stroke[49;50;53] and total cancer [54;64] in previous studies.

Future studies are necessary to confirm our finding of modifying effects of the Ca/Mg ratio and to define the optimal Ca/Mg intake ratio range. Our findings, if confirmed, will have a very important public health significance, including selecting optimal doses in the intervention trials and in the prevention strategy development for many common diseases. Furthermore, Ca/Mg ratio should be taken into account when the new RDA or DRI levels of Ca and Mg are

developed. For example, lower RDA or DRI levels of Mg for men and women may be required for Chinese populations because they have a low Ca/Mg intake ratio.

**Contributors**: DQ developed the hypothesis and the draft manuscript, and had primary responsibility for final content; WZ, XOS, and WHC designed, directed and obtained funding for the parent studies, and contributed to critical review of the paper; XD carried out the statistical analysis; HC contributed to the data analysis; GY, YTG and HL supervised field operations of the parent studies; MJS, YTG, XD, GY, BJ, YBX, HL and HC contributed to the critical review of the paper.

**Source of Funding:** This study was supported by USPHS grant R37CA70867 and R01CA082729 from the National Institutes of Health. Part of Dr. Dai's effort on the study has been supported by R37CA70867, R01CA082729, R01 AT004660 and R01 CA149633 from National Cancer Institute, Department of Health and Human Services and AICR #08A074-REV from the American Institute for Cancer Research.

The funding sponsor had no role in study design, data collection, statistical analysis and result interpretation, the writing of the report, and the decision to submit for publication. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

**Competing interests:** None

**Data sharing**: No additional data available.

## ACKNOWLEDGMENTS

The authors would like to thank the participants and staff for the SWHS and SMHS. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## REFERENCE


(1) Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* 2001; 81(1):239-297.

(2) Hardwick LL, Jones MR, Brautbar N, Lee DB. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. *J Nutr* 1991; 121(1):13-23.

(3) Bussiere FI, Gueux E, Rock E, Mazur A, Rayssiguier Y. Protective effect of calcium deficiency on the inflammatory response in magnesium-deficient rats. *Eur J Nutr* 2002; 41(5):197-202.

(4) Norman DA, Fordtran JS, Brinkley LJ, Zerwekh JE, Nicar MJ, Strowig SM et al. Jejunal and ileal adaptation to alterations in dietary calcium: changes in calcium and magnesium absorption and pathogenetic role of parathyroid hormone and 1,25-dihydroxyvitamin D. *J Clin Invest* 1981; 67(6):1599-1603.

(5) Nielsen FH, Milne DB, Gallagher S, Johnson L, Hoverson B. Moderate magnesium deprivation results in calcium retention and altered potassium and phosphorus excretion by postmenopausal women. *Magnes Res* 2007; 20(1):19-31.

(6) Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J* 1984; 108(1):188-193.

(7) SEELIG MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. *Magnes Res* 1990; 3(3):197-215.

(8) Flatman PW. Mechanisms of magnesium transport. *Annu Rev Physiol* 1991; 53:259-271.

(9) Hoenderop JG, Bindels RJ. Epithelial Ca2+ and Mg2+ channels in health and disease. *J Am Soc Nephrol* 2005; 16(1):15-26.

(10) Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE et al. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007; 86(3):743-751.

(11) Dai Q, Sandler RS, Barry EL, Summers RW, Grau MV, Baron JA. Calcium, Magnesium, and Colorectal Adenoma Recurrence: Results from a Randomized Trial . Epidemiology. In press 2012.

(12) Dai Q, Motley SS, Smith JA, Jr., Concepcion R, Barocas D, Byerly S et al. Blood magnesium, and the interaction with calcium, on the risk of high-grade prostate cancer. *PLoS One* 2011; 6(4):e18237.

(13) Manolio TA, Savage PJ, Burke GL, Hilner JE, Liu K, Orchard TJ et al. Correlates of fasting insulin levels in young adults: the CARDIA study. *J Clin Epidemiol* 1991; 44(6):571-578.

(14) Ziegler D. Type 2 diabetes as an inflammatory cardiovascular disorder. *Curr Mol Med* 2005; 5(3):309-322.

(15) He K, Liu K, Daviglus ML, Morris SJ, Loria CM, van HL et al. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; 113(13):1675-1682.

(16) Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 1992; 55(5):1018-1023.

(17) Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004; 27(1):134-140.

(18) Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27(1):59-65.

(19) Singh RB. Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnes Trace Elem* 1990; 9(3):143-151.

(20) Al Delaimy WK, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Magnesium intake and risk of coronary heart disease among men. *J Am Coll Nutr* 2004; 23(1):63-70.

(21) Dong JY, Xun P, He K, Qin LQ. Magnesium Intake and Risk of Type 2 Diabetes: Meta-analysis of prospective cohort studies. *Diabetes Care* 2011; 34(9):2116-2122.

(22) Larsson SC, Bergkvist L, Wolk A. Magnesium intake in relation to risk of colorectal cancer in women. *JAMA* 2005; 293(1):86-89.

(23) Folsom AR, Hong CP. Magnesium intake and reduced risk of colon cancer in a prospective study of women. *Am J Epidemiol* 2006; 163(3):232-235.

(24) van den Brandt PA, Smits KM, Goldbohm RA, Weijenberg MP. Magnesium intake and colorectal cancer risk in the Netherlands Cohort Study. *Br J Cancer* 2007; 96(3):510-513.

(25) Cai H, Shu XO, Hebert JR, Jin F, Yang G, Liu DK et al. Variation in nutrient intakes among women in Shanghai, China. *Eur J Clin Nutr* 2004; 58(12):1604-1611.

(26) Cai H, Yang G, Xiang YB, Hebert JR, Liu DK, Zheng W et al. Sources of variation in nutrient intakes among men in Shanghai, China. *Public Health Nutr* 2005; 8(8):1293-1299.

(27) Ervin RB, Wang CY, Wright JD, Kennedy-Stephenson J. Dietary intake of selected minerals for the United States population: 1999-2000. *Adv Data* 2004;(341):1-5.

(28) SEELIG MS. THE REQUIREMENT OF MAGNESIUM BY THE NORMAL ADULT. SUMMARY AND ANALYSIS OF PUBLISHED DATA. *Am J Clin Nutr* 1964; 14:242-290.

(29) Spencer H, Fuller H, Norris C, Williams D. Effect of magnesium on the intestinal absorption of calcium in man. *J Am Coll Nutr* 1994; 13(5):485-492.

(30) Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol* 2005; 162(11):1123-1131.

(31) Cai H, Shu XO, Gao YT, Li H, Yang G, Zheng W. A prospective study of dietary patterns and mortality in Chinese women. *Epidemiology* 2007; 18(3):393-401.

(32) Dai Q, Shu XO, Li H, Yang G, Shrubsole MJ, Cai H et al. Is green tea drinking associated with a later onset of breast cancer? *Ann Epidemiol* 2010; 20(1):74-81.

(33) Zhang X, Shu XO, Xiang YB, Yang G, Li H, Gao J et al. Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. *Am J Clin Nutr* 2011; 94(1):240-246.

(34) Rao C, Yang G, Hu J, Ma J, Xia W, Lopez AD. Validation of cause-of-death statistics in urban China. *Int J Epidemiol* 2007; 36(3):642-651.

(35) Villegas R, Yang G, Liu D, Xiang YB, Cai H, Zheng W et al. Validity and reproducibility of the food-frequency questionnaire used in the Shanghai men's health study. *Br J Nutr* 2007; 97(5):993-1000.

(36) Shu XO, Yang G, Jin F, Liu D, Kushi L, Wen W et al. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. *Eur J Clin Nutr* 2003; 58(1):17-23.

(37) Hosmer DW, Lemeshow S. Applied survival analysis. Regression modeling of time to even data. New York: Wiley; 1999.

(38) Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997; 145(1):72-80.

(39) Berridge MJ, Bootman MD, Lipp P. Calcium--a life and death signal. *Nature* 1998; 395(6703):645-648.

(40) Bootman MD, Berridge MJ. The elemental principles of calcium signaling. *Cell* 1995; 83(5):675-678.

(41) Schlingmann KP, Konrad M, Seyberth HW. Genetics of hereditary disorders of magnesium homeostasis. *Pediatr Nephrol* 2004; 19(1):13-25.

(42) Hans CP, Chaudhary DP, Bansal DD. Effect of magnesium supplementation on oxidative stress in alloxanic diabetic rats. *Magnes Res* 2003; 16(1):13-19.

(43) Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesauro P, Varricchio M et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992; 55(6):1161-1167.

(44) Wolf FI, Maier JA, Nasulewicz A, Feillet-Coudray C, Simonacci M, Mazur A et al. Magnesium and neoplasia: From carcinogenesis to tumor growth and progression or treatment. *Arch Biochem Biophys* 2006.

(45) Wark PA, Lau R, Norat T, Kampman E. Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis. *Am J Clin Nutr* 2012.

(46) Wallace K, Baron JA, Cole BF, Sandler RS, Karagas MR, Beach MA et al. Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; 96(12):921-925.

(47) Zhang X, Giovannucci EL, Wu K, Smith-Warner SA, Fuchs CS, Pollak M et al. Magnesium intake, plasma C-peptide, and colorectal cancer incidence in US women: a 28-year follow-up study. *Br J Cancer* 2012; 106(7):1335-1341.

(48) Sahota O, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int* 2006; 17(7):1013-1021.

(49) Song Y, Manson JE, Cook NR, Albert CM, Buring JE, Liu S. Dietary magnesium intake and risk of cardiovascular disease among women. *Am J Cardiol* 2005; 96(8):1135-1141.

(50) Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *Am J Clin Nutr* 2012; 95(2):362-366.

(51) Zhang W, Iso H, Ohira T, Date C, Tamakoshi A. Associations of dietary magnesium intake with mortality from cardiovascular disease: The JACC study. *Atherosclerosis* 2012.

(52) Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med* 2006; 23(10):1050-1056.

(53) Wang L, Manson JE, Sesso HD. Calcium Intake and Risk of Cardiovascular Disease: A Review of Prospective Studies and Randomized Clinical Trials. *Am J Cardiovasc Drugs* 2012.

(54) Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, Wolk A. Dietary calcium and magnesium intake and mortality: a prospective study of men. *Am J Epidemiol* 2010; 171(7):801-807.

(55) Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. *JAMA* 2005; 294(18):2336-2341.

(56) Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011; 342:d2040.

(57) Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; 341:c3691.

(58) Giovannucci E. Diet, body weight, and colorectal cancer: a summary of the epidemiologic evidence. *J Womens Health (Larchmt )* 2003; 12(2):173-182.

(59) SEELIG MS, Altura BM, Altura BT. Benefits and risks of sex hormone replacement in postmenopausal women. *J Am Coll Nutr* 2004; 23(5):482S-496S.

(60) Rosanoff A. Rising Ca:Mg intake ratio from food in USA Adults: a concern? *Magnes Res* 2010; 23(4):S181-S193.

(61) Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 1998; 136(3):480-490.

(62) Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. *Circulation* 2001; 103(3):462-468.

(63) Parkin DM, Whelen SL, Ferlay J, Raymond L. Cancer Incidence in Five Continents. [7]. 1997. Lyon, International Agency for Research on Cancer.

(64) Li K, Kaaks R, Linseisen J, Rohrmann S. Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg). *Cancer Causes Control* 2011.

Table 1. Baseline Lifestyle Factors and Demographics by Intakes of calcium and magnesium, the Shanghai Women's Health Study(SWHS) and the Shanghai Men Health Study (SMHS), 1996-2009

| | Calcium (mg/day) | | | Magnesium (mg/day) | | |
|---|---|---|---|---|---|---|
| **Shanghai Women's Health Study** | | | | | | |
| | <408 | 408-<600 | >=600 | <251 | 251-<320 | >=320 |
| **Married, %** | 87.87 | 90.28 | 88.45 | 87.93 | 89.87 | 88.96 |
| **Smokers, %** | 3.64 | 2.13 | 2.07 | 3.41 | 2.18 | 2.5 |
| **Alcohol drinkers, %** | 2.08 | 2.17 | 2.7 | 2.11 | 2.08 | 2.7 |
| **Tea drinker, %** | 24.84 | 32.23 | 36.22 | 26.09 | 31.4 | 34.24 |
| **Ginseng use, %** | 25.01 | 30.35 | 34.85 | 26.75 | 29.94 | 31.55 |
| **Ca Supplement use, %** | 15.41 | 20.33 | 25.09 | 17.49 | 19.75 | 21.43 |
| **Multivitamin use, %** | 3.98 | 8.1 | 11.68 | 5.74 | 7.52 | 8.77 |
| **Physically active, %** | 30.12 | 36.06 | 43.32 | 31.78 | 35.64 | 39.79 |
| **High school or up , %** | 8.75 | 15.55 | 19.78 | 10.82 | 15.2 | 15.77 |
| **Age (years), mean (SD)** | 53.37(9.45) | 51.88(8.79) | 51.85(8.54) | 53.48(9.55) | 51.95(8.74) | 51.68(8.45) |
| **BMI(kg/m2), mean (SD)** | 24.18(3.53) | 23.83(3.36) | 23.96(3.28) | 23.85(3.46) | 24.00(3.38) | 24.29(3.40) |
| **Daily nutrient intake adjusted for age and total energy, except for total energy** | | | | | | |
| **Total energy** | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) |
| **Saturated fat** | 7.02(0.02) | 8.99(0.02) | 10.99(0.03) | 7.89(0.02) | 8.62(0.02) | 9.65(0.03) |
| **Fiber** | 9.55(0.02) | 11.15(0.02) | 13.51(0.03) | 8.26(0.02) | 11.17(0.02) | 15.26(0.03) |
| **Phosphorus** | 852.77(0.63) | 985.46(0.66) | 1162.48(0.91) | 843.66(0.85) | 975.56(0.77) | 1161.18(1.16) |
| **Calcium** | 310.97(0.54) | 493.36(0.57) | 726.90(0.78) | 335.37(0.99) | 476.36(0.90) | 668.24(1.34) |
| **Magnesium** | 246.51(0.21) | 279.27(0.22) | 329.68(0.30) | 231.88(0.23) | 278.50(0.21) | 347.30(0.31) |
| **Retinol** | 146.88(0.95) | 186.49(1.00) | 228.98(1.37) | 163.43(1.14) | 178.50(1.03) | 203.98(1.55) |
| **Vitamin E** | 10.72(0.02) | 13.68(0.03) | 18.63(0.03) | 9.87(0.03) | 13.61(0.03) | 19.39(0.04) |
| **Folate** | 254.15(0.43) | 295.56(0.45) | 356.16(0.62) | 227.05(0.47) | 296.25(0.43) | 391.14(0.64) |
| **Sodium** | 252.92(0.52) | 355.20(0.55) | 489.11(0.75) | 260.13(0.73) | 345.16(0.67) | 467.53(1.00) |
| **Potassium** | 1479.84(2.17) | 1826.56(2.28) | 2293.21(3.14) | 1360.48(2.48) | 1808.59(2.25) | 2440.75(3.38) |
| **Zinc** | 10.20(0.01) | 10.85(0.01) | 11.84(0.01) | 10.02(0.01) | 10.83(0.01) | 12.02(0.01) |
| **Shanghai Men's Health Study** | | | | | | |
| **Married, %** | 96.37 | 97.37 | 97.70 | 96.48 | 97.44 | 97.57 |
| **Smokers, %** | 76.18 | 70.32 | 65.45 | 72.67 | 69.22 | 68.34 |
| **Alcohol drinkers, %** | 35.66 | 33.56 | 32.74 | 37.01 | 32.52 | 32.88 |
| **Tea drinker, %** | 64.96 | 66.92 | 68.45 | 64.3 | 67.47 | 68.3 |
| **Ginseng use, %** | 26.27 | 30.99 | 36.7 | 29.24 | 31.99 | 34.14 |
| **Ca Supplement use, %** | 3.07 | 4.36 | 5.91 | 4.02 | 4.67 | 5.11 |
| **Multivitamin use, %** | 3.92 | 6.92 | 10.04 | 6.00 | 7.58 | 8.32 |
| **Physically active, %** | 28.03 | 33.68 | 41.16 | 31.45 | 34.69 | 38.28 |
| **High school or up, %** | 14.39 | 22.37 | 29.02 | 19.14 | 23.91 | 25.07 |
| **Age (years), mean (SD)** | 55.90(10.27) | 55.28(9.73) | 55.17(9.43) | 56.91(10.58) | 55.56(9.70) | 54.46(9.20) |
| **BMI(kg/m2), mean (SD)** | 23.47(3.18) | 23.67(3.09) | 23.90(3.00) | 23.25(3.16) | 23.64(3.04) | 24.02(3.03) |
| **Daily nutrient intake adjusted for age and total energy, except for total energy** | | | | | | |
| **Total energy** [a] | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) |
| **Saturated fat** | 8.16(0.03) | 9.74(0.03) | 11.85(0.03) | 9.59(0.04) | 9.92(0.03) | 10.88(0.03) |
| **Fiber** | 9.27(0.03) | 10.72(0.02) | 13.28(0.02) | 8.17(0.03) | 10.32(0.02) | 14.02(0.02) |
| **Phosphorus** | 956.75(1.17) | 1081.00(0.93) | 1271.73(0.87) | 953.79(1.56) | 1071.31(1.08) | 1270.89(1.11) |
| **Calcium** | 340.34(1.12) | 512.58(0.89) | 778.31(0.83) | 379.76(1.83) | 518.93(1.27) | 740.23(1.30) |
| **Magnesium** | 271.18(0.37) | 303.34(0.30) | 359.14(0.28) | 258.30(0.45) | 297.74(0.31) | 367.15(0.32) |
| **Retinol** | 120.06(1.17) | 154.78(0.93) | 198.50(0.87) | 142.50(1.41) | 156.14(0.98) | 183.74(1.00) |
| **Vitamin E** | 10.72(0.04) | 13.48(0.03) | 18.43(0.03) | 10.13(0.05) | 13.15(0.03) | 18.73(0.04) |
| **Folate** | 271.83(0.75) | 319.26(0.60) | 398.67(0.56) | 245.92(0.87) | 308.91(0.61) | 415.67(0.62) |
| **Sodium** | 250.29(0.92) | 345.02(0.73) | 489.36(0.68) | 271.89(1.28) | 345.24(0.89) | 470.94(0.91) |
| **Potassium** | 1464.92(3.41) | 1778.86(2.70) | 2289.70(2.53) | 1399.54(4.28) | 1739.67(2.97) | 2326.91(3.04) |
| **Zinc** | 11.54(0.01) | 12.23(0.01) | 13.40(0.01) | 11.38(0.01) | 12.13(0.01) | 13.50(0.01) |

[a] adjusted for age only.

**Table 2 Hazard Ratios (HRs) for Total Mortality, and Mortality due to Cardiovascular Diseases and Cancer by Tertiles of Calcium and Magnesium in Shanghai Women**

| | Calcium intake (mg/day) | | | | | Magnesium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | P for trend | P for interaction | <251 | 251-<320 | ≥320 | P for trend | [a] P for interaction |
| Person years | 349874.66 | 281646.4664 | 175026.4882 | | | 335378.89 | 271235.7235 | 199933.001 | | |
| **Total Mortality** | | | | | | | | | | |
| Cases | 2019 | 1155 | 632 | | | 1992 | 1108 | 706 | | |
| Model 1 | 1.00 | 1.04(0.95,1.15) | 1.06(0.92,1.22) | 0.39 | | 1.00 | 1.04(0.94,1.16) | 1.09(0.94,1.27) | 0.270 | |
| Model 2 | 1.00 | 1.05(0.96,1.16) | 1.08(0.94,1.25) | 0.25 | 0.54 | 1.00 | 1.04(0.94,1.15) | 1.09(0.94,1.27) | 0.27 | 0.07 |
| [a] Ratio<=1.7 | 1.00 | 0.99(0.86,1.13) | 1.03(0.78,1.36) | 0.99 | | 1.00 | 1.14(1.00,1.30) | 1.24(1.02,1.51) | 0.02 | |
| [a] Ratio>1.7 | 1.00 | 1.03(0.85,1.24) | 1.06(0.81,1.39) | 0.68 | | 1.00 | 0.90(0.76,1.06) | 0.88(0.68,1.13) | 0.31 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | |
| Cases | 649 | 321 | 177 | | | 625 | 311 | 211 | | |
| Model 1 | 1.00 | 1.03(0.86,1.22) | 1.08(0.84,1.40) | 0.57 | | 1.00 | 1.11(0.92,1.34) | 1.35(1.03,1.77) | 0.04 | |
| Model 2 | 1.00 | 1.03(0.86,1.22) | 1.08(0.83,1.40) | 0.57 | 0.18 | 1.00 | 1.11(0.92,1.34) | 1.35(1.03,1.77) | 0.04 | 0.09 |
| [a] Ratio<=1.7 | 1.00 | 1.01(0.79,1.30) | 1.21(0.74,1.99) | 0.61 | | 1.00 | 1.17(0.93,1.48) | 1.53(1.08,2.16) | 0.02 | |
| [a] Ratio>1.7 | 1.00 | 0.95(0.67,1.35) | 1.07(0.64,1.79) | 0.69 | | 1.00 | 1.01(0.74,1.39) | 1.14(0.71,1.85) | 0.60 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | |
| Cases | 284 | 148 | 79 | | | 290 | 129 | 92 | | |
| Model 1 | 1.00 | 1.01(0.78,1.31) | 1.01(0.69,1.49) | 0.94 | | 1.00 | 0.96(0.73,1.28) | 1.19(0.79,1.78) | 0.46 | |
| Model 2 | 1.00 | 1.02(0.78,1.32) | 1.04(0.71,1.54) | 0.84 | 0.21 | 1.00 | 0.96(0.73,1.28) | 1.19(0.79,1.79) | 0.46 | 0.02 |
| [a] Ratio<=1.7 | 1.00 | 0.97(0.67,1.42) | 1.92(1.00,3.70) | 0.27 | | 1.00 | 1.01(0.70,1.46) | 1.69(1.02,2.80) | 0.07 | |
| [a] Ratio>1.7 | 1.00 | 0.86(0.53,1.40) | 0.85(0.41,1.76) | 0.68 | | 1.00 | 0.92(0.59,1.45) | 0.86(0.43,1.74) | 0.68 | |
| **Mortality due to Stroke** | | | | | | | | | | |
| Cases | 365 | 173 | 98 | | | 335 | 182 | 119 | | |
| Model 1 | 1.00 | 1.04(0.82,1.32) | 1.13(0.80,1.60) | 0.50 | | 1.00 | 1.25(0.97,1.61) | 1.50(1.03,2.16) | 0.03 | |
| Model 2 | 1.00 | 1.03(0.81,1.31) | 1.11(0.78,1.57) | 0.59 | 0.49 | 1.00 | 1.25(0.97,1.60) | 1.50(1.03,2.17) | 0.03 | 0.81 |
| [a] Ratio<=1.7 | 1.00 | 1.05(0.76,1.44) | 0.72(0.33,1.58) | 0.79 | | 1.00 | 1.30(0.95,1.77) | 1.40(0.87,2.23) | 0.12 | |
| [a] Ratio>1.7 | 1.00 | 1.07(0.65,1.77) | 1.35(0.66,2.77) | 0.34 | | 1.00 | 1.14(0.73,1.78) | 1.46(0.75,2.85) | 0.26 | |
| **Mortality due to all Cancers** | | | | | | | | | | |
| Cases | 789 | 556 | 271 | | | 756 | 537 | 323 | | |
| Model 1 | 1.00 | 1.09(0.95,1.26) | 0.90(0.72,1.12) | 0.51 | | 1.00 | 1.05(0.90,1.23) | 0.89(0.70,1.14) | 0.42 | |
| Model 2 | 1.00 | 1.10(0.95,1.27) | 0.92(0.74,1.15) | 0.68 | 0.24 | 1.00 | 1.05(0.90,1.23) | 0.89(0.70,1.14) | 0.42 | 0.78 |
| [a] Ratio<=1.7 | 1.00 | 1.03(0.85,1.26) | 0.82(0.54,1.25) | 0.73 | | 1.00 | 1.19(0.98,1.46) | 1.13(0.83,1.54) | 0.35 | |
| [a] Ratio>1.7 | 1.00 | 1.28(0.93,1.77) | 0.99(0.64,1.55) | 0.42 | | 1.00 | 0.85(0.66,1.10) | 0.61(0.41,0.92) | 0.02 | |
| **Mortality due to Lung cancer** | | | | | | | | | | |
| Cases | 171 | 109 | 50 | | | 156 | 109 | 65 | | |
| Model 1 | 1.00 | 1.00(0.73,1.37) | 0.76(0.47,1.24) | 0.34 | | 1.00 | 1.14(0.80,1.61) | 1.01(0.59,1.71) | 0.93 | |
| Model 2 | 1.00 | 1.02(0.74,1.40) | 0.81(0.50,1.32) | 0.47 | 0.87 | 1.00 | 1.15(0.81,1.62) | 1.01(0.60,1.72) | 0.92 | 0.95 |
| [a] Ratio<=1.7 | 1.00 | 1.13(0.73,1.76) | 1.78(0.82,3.87) | 0.22 | | 1.00 | 1.45(0.94,2.24) | 1.65(0.87,3.15) | 0.11 | |
| [a] Ratio>1.7 | 1.00 | 0.87(0.42,1.81) | 0.36(0.13,1.02) | 0.01 | | 1.00 | 0.64(0.36,1.13) | 0.30(0.11,0.77) | 0.01 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality due to Colorectal cancer** | | | | | | | | | | |
| Cases | 109 | 76 | 48 | | | 96 | 77 | 60 | | |
| Model 1 | 1.00 | 0.89(0.60,1.30) | 0.76(0.43,1.34) | 0.34 | | 1.00 | 1.19(0.78,1.82) | 1.32(0.70,2.51) | 0.39 | |
| Model 2 | 1.00 | 0.87(0.60,1.28) | 0.73(0.41,1.29) | 0.28 | 0.49 | 1.00 | 1.20(0.79,1.84) | 1.34(0.70,2.54) | 0.37 | 0.19 |
| [a] Ratio<=1.7 | 1.00 | 1.11(0.66,1.86) | 0.63(0.19,2.08) | 0.84 | | 1.00 | 1.92(1.11,3.33) | 2.20(0.96,5.04) | 0.05 | |
| [a] Ratio>1.7 | 1.00 | 0.50(0.23,1.10) | 0.32(0.11,0.94) | 0.05 | | 1.00 | 0.58(0.30,1.13) | 0.56(0.20,1.53) | 0.25 | |
| **Mortality due to Gastric cancer** | | | | | | | | | | |
| Cases | 108 | 68 | 32 | | | 114 | 58 | 36 | | |
| Model 1 | 1.00 | 1.15(0.77,1.72) | 1.05(0.57,1.92) | 0.80 | | 1.00 | 0.83(0.54,1.28) | 0.77(0.40,1.50) | 0.42 | |
| Model 2 | 1.00 | 1.17(0.78,1.75) | 1.09(0.59,2.03) | 0.69 | 0.23 | 1.00 | 0.83(0.54,1.28) | 0.77(0.40,1.50) | 0.42 | 0.33 |
| [a] Ratio<=1.7 | 1.00 | 0.75(0.42,1.35) | 1.34(0.47,3.77) | 0.81 | | 1.00 | 0.65(0.37,1.16) | 0.95(0.42,2.15) | 0.72 | |
| [a] Ratio>1.7 | 1.00 | 3.41(1.30,8.99) | 3.92(1.05,14.68) | 0.10 | | 1.00 | 1.10(0.54,2.23) | 0.63(0.20,2.01) | 0.49 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.
In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.
[a] Model 2 was used .

**Table 3 Hazard Ratios (HRS) for Total Mortality, and Mortality due to Cardiovascular Diseases by Tertiles of Calcium and Magnesium among men in Shanghai**

| | Calcium intake (mg/day) | | | | | Magnesium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | p for trend | p for interaction | <251 | 251-<320 | ≥320 | p for trend | p for interaction |
| Person years | 77215.85 | 112600.73 | 147167.01 | | | 74633.02 | 109118.9 | 153231.68 | | |
| **Total Mortality** | | | | | | | | | | |
| Cases | 820 | 798 | 800 | | | 904 | 715 | 799 | | |
| Model 1 | 1.00 | 0.88(0.77,1.01) | 0.79(0.66,0.95) | 0.01 | | 1.00 | 0.80(0.70,0.93) | 0.87(0.70,1.07) | 0.23 | |
| Model 2 | 1.00 | 0.90(0.78,1.02) | 0.82(0.68,0.99) | 0.04 | 0.01 | 1.00 | 0.81(0.70,0.93) | 0.87(0.71,1.07) | 0.23 | 0.19 |
| [a]Ratio<=1.7 | 1.00 | 0.97(0.79,1.18) | 0.95(0.66,1.36) | 0.73 | | 1.00 | 0.98(0.79,1.21) | 1.23(0.90,1.69) | 0.19 | |
| [a]Ratio>1.7 | 1.00 | 0.70(0.56,0.89) | 0.59(0.44,0.80) | 0.00 | | 1.00 | 0.69(0.57,0.84) | 0.66(0.50,0.88) | 0.01 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | |
| Cases | 305 | 273 | 222 | | | 323 | 246 | 231 | | |
| Model 1 | 1.00 | 0.91(0.72,1.14) | 0.72(0.52,0.99) | 0.04 | | 1.00 | 0.87(0.68,1.11) | 0.83(0.58,1.20) | 0.33 | |
| Model 2 | 1.00 | 0.93(0.74,1.16) | 0.75(0.54,1.04) | 0.08 | 0.03 | 1.00 | 0.88(0.68,1.12) | 0.84(0.58,1.21) | 0.35 | 0.07 |
| [a]Ratio<=1.7 | 1.00 | 1.01(0.73,1.40) | 0.92(0.49,1.70) | 0.90 | | 1.00 | 1.17(0.83,1.66) | 1.02(0.60,1.73) | 0.91 | |
| [a]Ratio>1.7 | 1.00 | 0.91(0.59,1.40) | 0.73(0.42,1.29) | 0.19 | | 1.00 | 0.66(0.47,0.94) | 0.66(0.39,1.11) | 0.12 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | |
| Cases | 137 | 143 | 115 | | | 155 | 118 | 122 | | |
| Model 1 | 1.00 | 0.91(0.66,1.26) | 0.63(0.40,1.00) | 0.05 | | 1.00 | 0.69(0.49,0.98) | 0.64(0.38,1.08) | 0.10 | |
| Model 2 | 1.00 | 0.93(0.67,1.29) | 0.66(0.42,1.06) | 0.08 | 0.09 | 1.00 | 0.70(0.49,0.99) | 0.65(0.38,1.09) | 0.11 | 0.54 |
| [a]Ratio<=1.7 | 1.00 | 1.16(0.72,1.86) | 1.64(0.73,3.70) | 0.28 | | 1.00 | 1.01(0.61,1.68) | 0.91(0.42,1.96) | 0.81 | |
| [a]Ratio>1.7 | 1.00 | 0.88(0.47,1.65) | 0.48(0.21,1.09) | 0.02 | | 1.00 | 0.48(0.30,0.78) | 0.43(0.21,0.88) | 0.02 | |
| **Mortality due to Stroke** | | | | | | | | | | |
| Cases | 168 | 130 | 107 | | | 168 | 128 | 109 | | |
| Model 1 | 1.00 | 0.91(0.66,1.24) | 0.81(0.52,1.26) | 0.35 | | 1.00 | 1.08(0.77,1.53) | 1.06(0.63,1.76) | 0.84 | |
| Model 2 | 1.00 | 0.92(0.67,1.27) | 0.85(0.54,1.33) | 0.47 | 0.19 | 1.00 | 1.09(0.77,1.54) | 1.06(0.63,1.77) | 0.83 | 0.06 |
| [a]Ratio<=1.7 | 1.00 | 0.90(0.58,1.41) | 0.42(0.15,1.19) | 0.21 | | 1.00 | 1.32(0.82,2.12) | 1.08(0.52,2.24) | 0.78 | |
| [a]Ratio>1.7 | 1.00 | 0.99(0.54,1.80) | 1.20(0.54,2.65) | 0.52 | | 1.00 | 0.93(0.56,1.54) | 1.02(0.48,2.16) | 0.94 | |
| **Mortality due to all Cancers** | | | | | | | | | | |
| Cases | 320 | 337 | 394 | | | 335 | 316 | 400 | | |
| Model 1 | 1.00 | 0.86(0.70,1.05) | 0.79(0.60,1.04) | 0.10 | | 1.00 | 0.84(0.68,1.04) | 0.93(0.68,1.28) | 0.74 | |
| Model 2 | 1.00 | 0.87(0.71,1.06) | 0.81(0.61,1.07) | 0.14 | 0.23 | 1.00 | 0.84(0.68,1.05) | 0.93(0.68,1.29) | 0.75 | 0.97 |
| Ratio<=1.7 | 1.00 | 0.88(0.65,1.20) | 0.73(0.42,1.27) | 0.26 | | 1.00 | 0.93(0.66,1.30) | 1.31(0.80,2.13) | 0.26 | |
| Ratio>1.7 | 1.00 | 0.68(0.47,0.98) | 0.59(0.37,0.93) | 0.05 | | 1.00 | 0.80(0.60,1.06) | 0.74(0.49,1.14) | 0.19 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.

In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[a] Model 2 was used .

**Table 4 Hazard Ratios (HRS) for Total Mortality, and Mortality due to Cardiovascular Diseases by quartiles of Calcium and Magnesium intake among men in Shanghai**

| | Calcium intake (mg/day) | | | | | | Magnesium intake (mg/day) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408- | 600- | 800- | p for trend | p for interaction | <251 | 251- | 320- | 420- | p for trend | p for interaction |
| Person years | 77215.85 | 112600.73 | 90733.06 | 56433.95 | | | 74633.02 | 109118.90 | 108337.41 | 44894.27 | | |
| **Total Mortality** | | | | | | | | | | | | |
| Cases | 820 | 798 | 486 | 314 | | | 904 | 715 | 564 | 235 | | |
| Model 1 | 1.00 | 0.93(0.81,1.06) | 0.79(0.66,0.95) | 1.03(0.80,1.31) | 0.50 | | 1.00 | 0.89(0.77,1.04) | 0.96(0.77,1.19) | 1.40(1.02,1.93) | 0.13 | |
| Model 2 | 1.00 | 0.95(0.83,1.09) | 0.83(0.69,1.00) | 1.12(0.87,1.44) | 0.97 | 0.01 | 1.00 | 0.89(0.77,1.04) | 0.96(0.78,1.20) | 1.41(1.02,1.93) | 0.13 | 0.19 |
| [a]Ratio<=1.7 | 1.00 | 0.96(0.79,1.17) | 0.98(0.68,1.40) | 0.70(0.29,1.68) | 0.63 | | 1.00 | 0.99(0.79,1.23) | 1.24(0.90,1.70) | 1.30(0.79,2.13) | 0.14 | |
| [a]Ratio>1.7 | 1.00 | 0.80(0.63,1.02) | 0.69(0.50,0.95) | 0.97(0.64,1.48) | 0.87 | | 1.00 | 0.84(0.68,1.03) | 0.83(0.61,1.13) | 1.39(0.89,2.17) | 0.48 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | | | |
| Cases | 305 | 273 | 135 | 87 | | | 323 | 246 | 168 | 63 | | |
| Model 1 | 1.00 | 0.94(0.75,1.19) | 0.70(0.51,0.97) | 0.91(0.59,1.40) | 0.21 | | 1.00 | 0.93(0.72,1.20) | 0.88(0.61,1.28) | 1.20(0.69,2.08) | 0.95 | |
| Model 2 | 1.00 | 0.97(0.77,1.23) | 0.74(0.53,1.03) | 1.01(0.65,1.57) | 0.42 | 0.03 | 1.00 | 0.94(0.72,1.21) | 0.88(0.61,1.28) | 1.19(0.69,2.07) | 0.94 | 0.07 |
| [a]Ratio<=1.7 | 1.00 | 1.01(0.73,1.40) | 0.93(0.50,1.74) | 0.80(0.18,3.57) | 0.86 | | 1.00 | 1.19(0.84,1.70) | 1.02(0.60,1.74) | 1.18(0.51,2.74) | 0.89 | |
| [a]Ratio>1.7 | 1.00 | 1.05(0.67,1.65) | 0.86(0.48,1.56) | 1.31(0.61,2.82) | 0.70 | | 1.00 | 0.74(0.51,1.08) | 0.75(0.43,1.31) | 1.05(0.46,2.39) | 0.89 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | | | |
| Cases | 137 | 143 | 70 | 45 | | | 155 | 118 | 81 | 41 | | |
| Model 1 | 1.00 | 0.94(0.68,1.31) | 0.63(0.39,1.00) | 0.75(0.41,1.39) | 0.12 | | 1.00 | 0.79(0.54,1.14) | 0.72(0.42,1.23) | 1.18(0.54,2.56) | 0.88 | |
| Model 2 | 1.00 | 0.97(0.70,1.35) | 0.66(0.41,1.06) | 0.83(0.44,1.56) | 0.22 | 0.09 | 1.00 | 0.80(0.55,1.15) | 0.73(0.42,1.24) | 1.18(0.55,2.56) | 0.89 | 0.54 |
| [a]Ratio<=1.7 | 1.00 | 1.15(0.72,1.85) | 1.69(0.75,3.81) | 1.02(0.12,8.52) | 0.33 | | 1.00 | 1.05(0.62,1.77) | 0.92(0.43,2.00) | 1.20(0.37,3.92) | 0.99 | |
| [a]Ratio>1.7 | 1.00 | 0.94(0.49,1.82) | 0.52(0.22,1.20) | 0.63(0.21,1.86) | 0.14 | | 1.00 | 0.59(0.35,1.00) | 0.55(0.25,1.20) | 0.96(0.31,2.95) | 0.67 | |
| **Mortality due to Stroke** | | | | | | | | | | | | |
| Cases | 168 | 130 | 65 | 42 | | | 168 | 128 | 87 | 22 | | |
| Model 1 | 1.00 | 0.95(0.69,1.31) | 0.79(0.50,1.24) | 1.08(0.59,1.98) | 0.80 | | 1.00 | 1.09(0.76,1.56) | 1.06(0.63,1.78) | 1.08(0.48,2.41) | 0.89 | |
| Model 2 | 1.00 | 0.97(0.70,1.35) | 0.83(0.52,1.31) | 1.19(0.64,2.21) | 0.97 | 0.19 | 1.00 | 1.09(0.76,1.57) | 1.06(0.63,1.78) | 1.07(0.48,2.40) | 0.89 | 0.06 |
| [a]Ratio<=1.7 | 1.00 | 0.91(0.58,1.41) | 0.39(0.13,1.20) | 0.65(0.08,5.30) | 0.22 | | 1.00 | 1.31(0.81,2.13) | 1.08(0.52,2.24) | 1.04(0.30,3.57) | 0.92 | |
| [a]Ratio>1.7 | 1.00 | 1.25(0.66,2.34) | 1.57(0.68,3.63) | 2.97(1.00,8.87) | 0.04 | | 1.00 | 0.93(0.54,1.60) | 1.02(0.46,2.25) | 1.02(0.31,3.40) | 0.90 | |
| **Mortality due to all Cancers** | | | | | | | | | | | | |
| Cases | 320 | 337 | 236 | 158 | | | 335 | 316 | 273 | 127 | | |
| Model 1 | 1.00 | 0.90(0.73,1.10) | 0.80(0.60,1.05) | 0.95(0.66,1.38) | 0.55 | | 1.00 | 0.97(0.77,1.23) | 1.10(0.78,1.54) | 1.68(1.03,2.74) | 0.07 | |
| Model 2 | 1.00 | 0.91(0.74,1.12) | 0.82(0.62,1.08) | 1.00(0.68,1.46) | 0.72 | 0.23 | 1.00 | 0.97(0.77,1.23) | 1.10(0.78,1.54) | 1.68(1.03,2.74) | 0.06 | 0.97 |
| [a]Ratio<=1.7 | 1.00 | 0.88(0.65,1.19) | 0.75(0.43,1.31) | 0.51(0.15,1.79) | 0.21 | | 1.00 | 0.93(0.65,1.32) | 1.31(0.80,2.15) | 1.33(0.62,2.84) | 0.22 | |
| [a]Ratio>1.7 | 1.00 | 0.73(0.50,1.08) | 0.65(0.40,1.04) | 0.78(0.42,1.46) | 0.74 | | 1.00 | 1.03(0.74,1.42) | 1.04(0.65,1.66) | 1.91(0.97,3.76) | 0.18 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.
In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.
[a] Model 2 was used .

Table 5. Hazard Ratios (HRS)[a] for Total Mortality by tertiles of calcium and magnesium intake among women and men stratified by the median intake of magnesium and calcium, respectively.

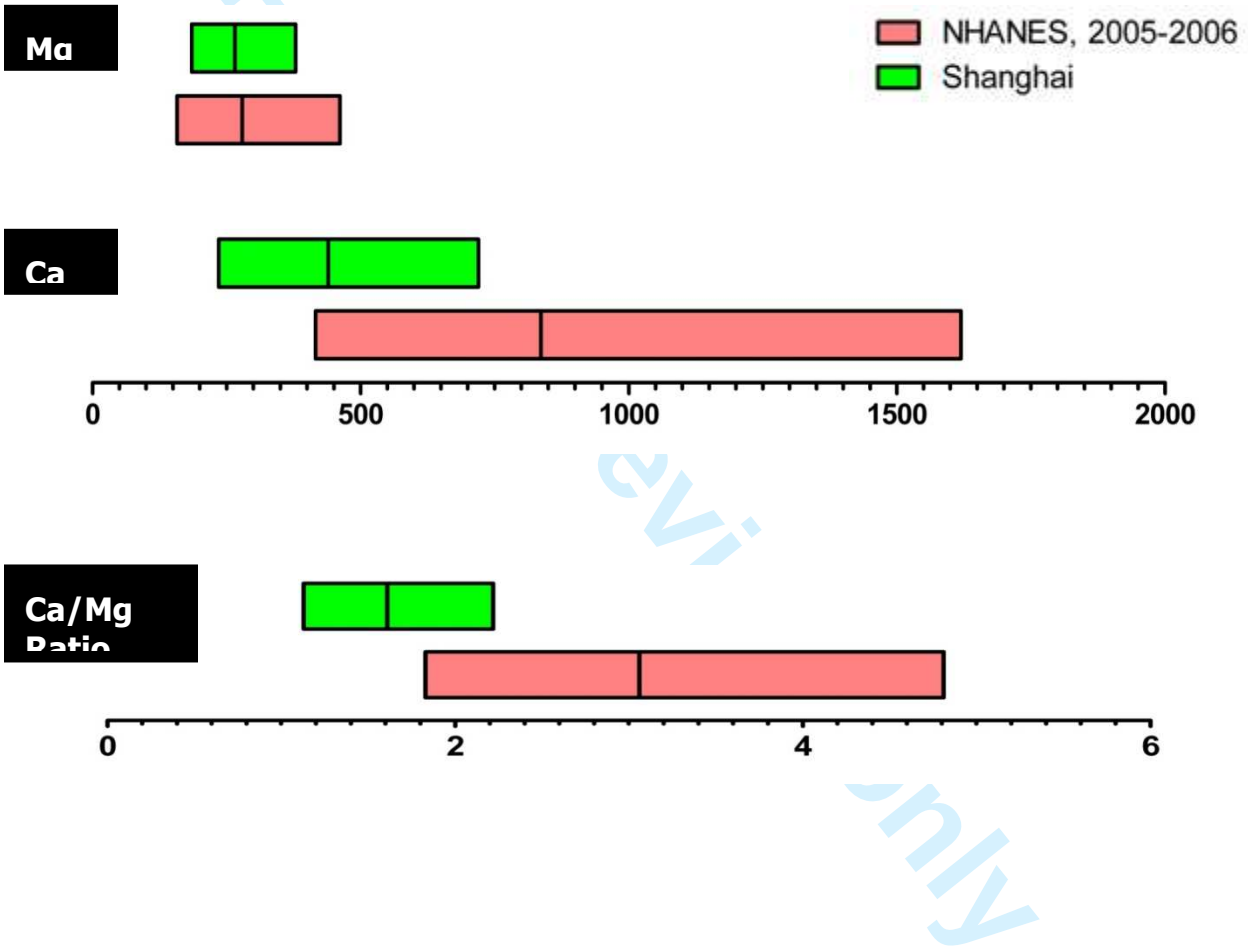
| | | Calcium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|
| | | <480 | 480-<600 | >=600 | p for trend | p for interaction |
| SWHS | All subjects | 1.00 | 1.05(0.96,1.16) | 1.08(0.94,1.25) | 0.25 | 0.42 |
| | [b]Mg<=284.3 | 1.00 | 1.06(0.95,1.19) | 1.19(0.93,1.52) | 0.15 | |
| | [b]Mg>284.3 | 1.00 | 0.84(0.69,1.03) | 0.82(0.64,1.05) | 0.19 | |
| SMHS | All subjects | 1.00 | 0.90(0.78,1.02) | 0.82(0.68,0.99) | 0.04 | 0.11 |
| | [b]Mg<=284.3 | 1.00 | 0.97(0.82,1.14) | 0.91(0.68,1.22) | 0.54 | |
| | [b]Mg>284.3 | 1.00 | 0.88(0.67,1.16) | 0.75(0.54,1.03) | 0.03 | |
| | | Magnesium intake (mg/day) | | | | |
| | | <251 | 251-<320 | >=320 | p for trend | p for interaction |
| SWHS | All subjects | 1.00 | 1.04(0.94,1.15) | 1.09(0.94,1.27) | 0.27 | 0.42 |
| | [c]Ca<=491 | 1.00 | 1.12(0.99,1.26) | 1.31(1.05,1.64) | 0.01 | |
| | [c]Ca>491 | 1.00 | 0.79(0.64,0.98) | 0.70(0.52,0.95) | 0.03 | |
| SMHS | All subjects | 1.00 | 0.81(0.70,0.93) | 0.87(0.71,1.07) | 0.23 | 0.11 |
| | [c]Ca<=491 | 1.00 | 1.00(0.82,1.21) | 1.59(1.15,2.20) | 0.06 | |
| | [c]Ca>491 | 1.00 | 0.70(0.55,0.88) | 0.57(0.42,0.79) | 0.00 | |

[a] Model 2 was used. age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted. Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[b] Mg= magnesium intake

[c] Ca= calcium intake

**Figure 1. Comparison of intake levels of Ca (mg/day), Mg (mg/day) and Ca/Mg ratio in US and Shanghai, China**



# Dietary Calcium and Magnesium, Calcium/magnesium Ratio, and Mortality: Results from the Shanghai Women's and Men's Health Studies

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2012-002111.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 06-Jan-2013 |
| Complete List of Authors: | Dai, Qi; Vanderbilt School of Medicine, Department of Medicine<br>Shu, Xiao-Ou; Vanderbilt School of Medicine, Department of Medicine<br>Deng, Xinqing; Vanderbilt School of Medicine, Department of Medicine<br>Xiang, Yong-bing; Shanghai Cancer Institute, Department of Epidemiology<br>Li, Honglan; Shanghai Cancer Institute, Department of Epidemiology<br>Yang, Gong; Vanderbilt School of Medicine, Department of Medicine<br>Shrubsole, Martha; Vanderbilt School of Medicine, Department of Medicine<br>Ji, Butian; National Institutes of Health, Division of Cancer Epidemiology and Genetics<br>Cai, Hui; Vanderbilt School of Medicine, Department of Medicine<br>Chow, Wong-Ho; National Institutes of Health, Division of Cancer Epidemiology and Genetics<br>Gao, Yu-Tang; Shanghai Cancer Institute, Department of Epidemiology<br>Zheng, Wei; Vanderbilt School of Medicine, Department of Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Nutrition and metabolism |
| Keywords: | Public health < INFECTIOUS DISEASES, EPIDEMIOLOGY, NUTRITION & DIETETICS |
| | |

**Original Research Article**

# Dietary Calcium and Magnesium, Calcium/magnesium Ratio, and Mortality: Results from the Shanghai Women's and Men's Health Studies

Qi Dai[1], Xiao-Ou Shu[1], Xinqing Deng[1], Yong-Bing Xiang[2], Honglan Li[2], Gong Yang[1], Martha J Shrubsole[1], Butian Ji[3], Hui Cai [1], Wong-Ho Chow[3,4], Yu-Tang Gao[2], Wei Zheng[1]

[1]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt School of Medicine, Nashville, TN, USA

[2]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[4]Department of Epidemiology, Division of Cancer Prevention and Population Sciences, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Dr. Qi Dai, Vanderbilt Epidemiology Center, Institute for Medicine & Public Health, Sixth Floor, Suite 600, 2525 West End Avenue, Nashville, TN 37203-1738

Phone: 615-936-0707, Fax: 615-936-8290, E-mail: qi.dai@vanderbilt.edu

**Running Title:** calcium/magnesium ratio and mortality

**Key words:** Magnesium, calcium, ratio, mortality, cancer and cardiovascular diseases

## ABSTRACT

**Objectives:** Magnesium (Mg) and calcium (Ca) antagonize each other in (re)absorption, inflammation and many other physiologic activities. Based on mathematical estimation, the absorbed number of Ca or Mg depends on the dietary ratio of Ca to Mg intake. We hypothesize that dietary Ca/Mg ratio modifies the effects of Ca and Mg on mortality due to gastrointestinal tract cancer, and perhaps, mortality due to diseases occurring in other organs or systems.

**Design, Setting, Participants:** We conducted analyses using data from two large population-based cohorts (Shanghai Women's and Men's Health Studies) conducted in China with over 130,000 participants.

**Primary outcome measures:** All-cause mortality and disease-specific mortality

**Results:** In this Chinese population with a low Ca/Mg intake ratio (a median of 1.7 vs. around 3.0 in US populations), intakes of Mg greater than US RDA levels (320mg/day among women and 420mg/day among men) were related to increased risks of total mortality for both women and men. Consistent with our hypothesis, Ca/Mg intake ratio significantly modified the associations of intakes of Ca and Mg with mortality risk whereas no significant interactions between Ca and Mg in relation to outcome were found. The associations differed by gender. Among men with Ca/Mg ratio >1.7, increased intakes of Ca and Mg were associated with reduced risks of total mortality, and mortality due to coronary heart diseases. In the same group, intake of Ca was associated with a reduced risk of mortality due to cancer. Among women with Ca/Mg ratio ≤1.7, intake of Mg was associated with increased risks of total mortality, and mortality due to cardiovascular diseases and colorectal cancer.

**Conclusions:** These results, if confirmed, may help to understand the optimal balance between Ca and Mg in the etiology and prevention of these common diseases and reduction in mortality.

## Article summary

*Article focus*

- Modifying effects of Ca/Mg intake ratio on the associations between intakes of Ca and Mg with disease mortality
- The effect of high Mg intake on disease mortality differs in populations with a very low Ca/Mg intake ratio from those (i.e. Western populations) with a high ratio
- Modifiying effects of sex on the associations between intakes of Ca and Mg with disease mortality

*Key messages*

- Significant modifying effects of combined Ca/Mg intake ratio, but not Mg or Ca intake alone, on the associations between intakes of Ca and Mg, respectively, with risk of total mortality and coronary heart diseases and possibly cancer
- In contrast to studies conducted in the US, high intake of Mg was related to an increased risk of total mortality among both men and women a similar Mg intake level but a low Ca/Mg intake ratio.
- Sex significantly modified the associations between intakes of Ca and Mg with disease mortality

*Strengths and limitations of this study*

- Population-based prospective design with large sample sizes
- High rates for baseline participation and follow-up

- A unique population with a similar Mg intake, but a lower Ca/Mg intake ratio vs. US population
- Adjustment for many potential confounding factors
- Similar results in sensitivity analysis by excluding those who used Ca or multivitamin supplements
- Caution for the generalization of findings to populations with a high Ca/Mg ratio
- The Ca and Mg contents of drinking water not included
- Small sample size in the analyses by cancer subtype, particularly among men

## INTRODUCTION

Magnesium (Mg) and calcium (Ca) belong to the same family in the periodic table and share the same homeostatic regulating system[1] involving Ca sensing receptor (CaSR) and (re)absorption[2]. Meanwhile, Mg and Ca antagonize each other in many physiologic activities [2-8]. It was not until recently that Mg was thought to share ion transporters with Ca in (re)absorption[9]. Mg ion transporters identified in recent years (e.g. TRPM7) also have affinity for Ca[9]. In the intestine, Ca and Mg may directly or indirectly compete for intestinal absorption [2]. A low concentration of Ca and a high concentration of Mg (thus, a low Ca:Mg) in the lumen activates mucosal transport of Mg [2]. A high Ca intake reduces absorption rates for both Mg and Ca in humans [2;4].

Colon lumen concentrations for $Ca^{2+}$ and $Mg^{2+}$ are monitored by the same receptor, the CaSR [1]. If the body needs to absorb a total of ten ions of Ca and Mg, and the diet contains five ions of Ca and five of Mg, all five Ca and five Mg ions are absorbed. If the diet consists of forty five Ca and five Mg, nine Ca and one Mg are absorbed. Thus, if the total absorbed number of Ca and Mg is relatively constant, the absorption number for Ca is dependent upon $Ca*(1/(Ca+Mg)) =Ca/(Mg+Ca)=(Mg/Ca +1)^{-1}$, in which solely the Mg/Ca ratio varies. It is also true for Mg. Thus, we postulated that the dietary ratio of Ca to Mg modifies the effects of Ca and Mg intakes on carcinogenesis [10;11]. In a study conducted in the US, we found high intake of total Ca or Mg may only be related to a reduced risk of colorectal adenoma when the Ca/Mg ratio was below 2.78 [10]. In a randomized clinical trial conducted in the US, Ca treatment only significantly reduced colorectal adenoma recurrence risk when the baseline dietary Ca/Mg ratio was under 2.63 and this effect modification by the Ca/Mg ratio cannot solely be attributed to the baseline dietary intake in either Ca or Mg[11]. In another study, high serum Ca/Mg ratio was associated with an

increased risk of high-grade prostate cancer after controlling for serum Ca and Mg[12]. However, all these studies have been conducted in high Ca/Mg ratio populations.

Many studies conducted in Western countries have linked low intake of Mg to insulin resistance[13] and systemic inflammation[14] and, thus, risk of diseases common in Western countries, such as metabolic syndrome [15], type II diabetes[16-18], coronary heart disease[19-21] and cancer[10;22-24]. East Asians have much lower incidence and mortality rates of coronary heart disease and colorectal cancer, but much higher rates of stroke compared to their counterparts in US. However, mean intake of Mg [25;26] in East Asia[10] is equivalent to the US population [27] whereas the Ca/Mg intake ratio is almost halved in the Chinese population compared to the US population [25;28]. Thus, it is possible that the differential Ca/Mg intake ratio may contribute, in part, to the different incidence and mortality rates of these common diseases[10].

The US population's low Ca/Mg ratio range defined as below US median) overlaps with the high ratio range in the Chinese population (above Chinese median) (See **Figure 1**). Thus, we further hypothesize that in Chinese populations, intakes of Mg and Ca may only be related to a reduced risk of mortality due to colorectal cancer and, perhaps, other common diseases when dietary Ca/Mg ratio is above median (1.7). Conversely, previous studies indicate that high Mg intake led to a negative Ca balance when Ca intake was low (i.e. low Ca/Mg ratio) [29]. Thus, high Mg intake may have a detrimental effect when Ca/Mg ratio is very low (below 1.7). We tested these hypotheses in two population-based cohorts conducted in China with over 130,000 participants.

## METHODS

***SWHS and SMHS:*** The Shanghai Women's Health Study (SWHS) and the Shanghai Men Health Study (SMHS) are two population-based, prospective cohort studies conducted in urban Shanghai, China. In both studies similar designs which were described in detail elsewhere, were utilized [30;31]. In brief, during 1996 and 2000, the SWHS recruited 74, 942 female participants aged 40 to 70 years from seven urban communities representative of urban Shanghai with a participation rate of 92.7% while from 2002 to 2006, the SMHS enrolled 61, 500 men aged 40 to 74 years from the same seven communities with a participation rate of 74.1%. Certified interviewers elicited information on demographic characteristics, medical history, anthropometrics, usual dietary habits, physical activities, and other lifestyle factors. At least two measurements were conducted for weight, height, and circumferences of the waist and hips at the in-person interview. The study was approved by all relevant institutional review boards in China (Shanghai Cancer Institute) and the United States (Vanderbilt University).

***Cohort follow-up and outcome ascertainment:*** The SWHS and SMHS participants have been followed-up by biennial home visit as well as annual record linkage to the population-based Shanghai Cancer Registry and Vital Statistics Registry. In the current study, the primary outcomes included deaths from all causes, deaths from cardiovascular diseases (including coronary heart diseases and stroke) and deaths from cancers occurring between the baseline recruitment and the most recent follow-up and/or annual vital status linkage. The follow-up rate for vital status in both cohorts was >99.9% complete[32;33]. In this analysis, in order to allow for the delay in records processing, the date of the last follow-up was set as Dec, 31, 2009 for study participants, 6 months before the most recent record linkage (June 30, 2010). The underlying

causes for deaths were determined based primarily on death certificates from Shanghai Vital Statistics Registry which are coded using the *International Classification of Diseases, Ninth Revision* (ICD-9). Studies have been conducted to validate cause-of-death statistics in urban China, which also includes urban Shanghai, and data on death certificates have shown reasonable accuracy for major causes of deaths including cancer and cardiovascular diseases [34].

***Exposure Measurement and Covariates:*** Usual dietary intakes were assessed through in-person interviews using validated food-frequency questionnaires (FFQs) (11,12) in SMHS[35] and SWHS[36]. Nutrient intakes (i.e. dietary Ca and Mg), were derived from FFQs using the Chinese food composition tables (Institute of Nutrition and Food Safety, China CDC, 2004). A wide array of covariates assessed at the baseline survey and FFQs were compared by levels of exposure (intake levels of Ca and Mg) as potential confounding factors (Table 1).

***Statistical Analysis*** To be consistent with SMHS, we excluded from the analysis 1,579 subjects with a history of cancer at baseline from the SWHS. We also excluded 126 subjects in SWHS and 70 in SMHS with unreasonably high or low energy intake (<500 or >3,500 kcal/day for women; <500 or >4,200 kcal/day for men), and 8 subjects in SWHS and 14 in SMHS who moved away from Shanghai immediately after the baseline survey. As a result, a total of 73,232 for SWHS and 61,414 for SMHS were included in the final analyses.

We estimated the main associations using hazard ratio (HR) in Cox proportional hazard regression models[37], using age at entry and age at death or age at censor as a time-scale[38]. To be consistent with previous cohort studies which evaluated the association of Ca and Mg with

disease risks[10;22;23], we have adjusted for the following potential confounding factors: age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng (yes, no), alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium and zinc. Log-transformation was conducted for continuous variables. We have adjusted for age to control for potential birth cohort effect. We have additionally adjusted for postmenopausal hormone use, but the associations did not change.

Determination of low, medium and high exposure categories: since intake level of Mg in our study population is comparable to the studies conducted in Western countries, we have used the US's Mg Recommended Daily Allowance (RDA) for women (320 mg/day), which is very close to the 66th percentile of Mg intake in our study population (321 mg/day), as the upper cutpoint. In contrast, very few study participants had a Ca intake level above the current US Daily Reference Intake (DRI) for Ca (1000 mg/day). Thus, we have used 600 mg/day, a previous Ca DRI for Chinese (Institute of Nutrition and Food Safety and Chinese Institute for Preventive Medicine, 1991), as the upper cutpoint. We utilized the medians of Mg and Ca for the remaining participants as the lower cutpoint. Since the intake levels of Mg and Ca in men were higher than women, we have added one cutpoint (i.e. US RDA for Mg in men (420 mg/day)) for Mg and one cutpoint (i.e. the current DRI for Ca in Chinese adults (800 mg/day)) for Ca in the analysis for men.

Separate analyses were conducted for SWHS (women) and SMHS (men). The first model was adjusted for age and other confounding factors except for Ca and Mg. In the second model, Ca

and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively. Stratified analyses by medians of Ca/Mg ratio[10;11], Ca or Mg intake[11] were conducted. In the stratified analyses, the full-adjusted (second) model was used. In addition, we have conducted sensitivity analyses by excluding those who took Ca supplement or multivitamin. Multiplicative interactions between continuous Mg or Ca and continuous Ca/Mg ratio were tested. Tests for trend across exposure categories were performed by entering the categorical variables as a continuous variable in the model. *P* values of $< 0.05$ (2-sided probability) were interpreted as being statistically significant. Statistical analyses were conducted by using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

## RESULTS

Selected demographic characteristics and potentially confounding factors were compared by intake levels of Ca and Mg separately for SWHS and SMHS as shown in **Table 1**. Proportions of participants with high educational achievement, female alcohol drinkers, tea drinkers, users of Ca, multivitamin and ginseng supplements, and those who were physically active and consumed high levels of (energy- and age-adjusted) saturated fatty acids, fiber, phosphorus, retinol, vitamin E, folate, sodium, potassium, zinc and Mg or Ca increased with increasing intakes of Ca and Mg. The proportion of participants that smoked, male alcohol drinkers, and those who were not married decreased with increasing intakes of Ca and Mg.

In the pooled analysis of SMHS and SWHS (Data not shown), we found that sex significantly modified the associations between intakes of Ca and Mg with risk of total mortality (*P* for

interactions < 0.01) and mortality due to cardiovascular diseases (*P* for interactions < 0.01). Sex also appeared to modify the associations of Ca and Mg with cancer (*P* for interactions were 0.125 for Mg and 0.280 for Ca, respectively). Thus, separate analyses were conducted for SWHS and SMHS.

Presented in **Table 2** are the associations of dietary intakes of Ca and Mg with risk of total mortality, mortality due to cardiovascular diseases and cancer in SWHS. After adjusting for potentially confounding factors (model 1) and additionally controlling for Ca or Mg, respectively (model 2), we found that among women, high intake of Mg was significantly associated with 35-50% increased risks of mortality due to cardiovascular diseases, particularly stroke. Furthermore, Ca/Mg ratio modified the associations between intake of Mg and risk of total mortality (*P* for interaction, 0.07) and mortality due to coronary heart diseases (*P* for interaction, 0.02) in model 2. Among those with Ca/Mg ratio ≤ 1.7, intake of Mg was significantly associated with 24% -66% increased risks of total mortality and mortality due to cardiovascular diseases (including stroke and coronary heart disease), and an 120% increased risk of colorectal cancer (P for trend, 0.05). On the other hand, among those with Ca/Mg intake ratio > 1.7, intake of Mg was related to a decreased risk of lung cancer (P for trend, 0.01); and intake of Ca was associated with significantly reduced risk of cancer (P for trend, 0.02) including lung cancer (P for trend, 0.01) and colorectal cancer (P for trend, 0.05), but was related to an increased risk of gastric cancer. We did not present the results for other GI tract cancers because the sample sizes for mortality due to these gastrointestinal tract cancers are sparse and not reliable. The findings were also not statistically significant. In the sensitivity analyses conducted by excluding those who used Ca or multivitamin supplements, similar results were observed (Data not shown).

We found the association patterns with Ca and Mg differed in women (SWHS) and men (SMHS). Because the differential associations could potentially be caused by use of different sex-specific cutpoints we chose to evaluate first the associations using common cutpoints (Tables 2 and 3). Thus, **Table 3** shows the associations between dietary intakes of Ca and Mg and risk of total mortality, mortality due to cardiovascular diseases and cancer in SMHS using the same cutpoints as those for women in SWHS (Table 2). Among men, high intake of Ca (≥600 mg/day) were related to reduced risks of total mortality and mortality due to cardiovascular diseases and, possibly, cancer while intake of Mg (≥320 mg/day) was possibly related to a reduced risk of death due to coronary heart diseases. In the stratified analysis (model 2), we found the associations between intakes of Ca and Mg and risk of total mortality and cardiovascular diseases were modified by Ca/Mg ratio with the *p* for interactions ranging from 0.01 to 0.07. Among participants with Ca/Mg intake ratio > 1.7, risks of total mortality, and mortality due to coronary heart disease and cancer were significantly reduced with increasing intakes of Ca and Mg. These associations were statistically significant except for the non-significant inverse association between Mg and cancer. In contrast, among those with Ca/Mg ratio ≤ 1.7, intakes of Ca and Mg were not significantly related to risks. The sample size became very sparse in the analysis for subtype cancers due to a shorter follow-up time for SMHS (men) compared to SWHS (women) and none of the associations was significant (Data not shown). Analyses limited to those who did not use Ca or multivitamin supplements generated similar results (Data not shown).

Men had higher intake levels of Ca and Mg than women. In **Table 4**, we repeated the analyses presented in Table 3, but added one cutpoint (420 mg/day, RDA for US men) for Mg and one cutpoint (800 mg/day, the current DRI for Chinese) for Ca. We found that highest intake of Mg (≥420 mg/day) was significantly associated with increased risks of total mortality and mortality due to cancer. We also found Ca intake levels between 600-800 mg/day, but not higher than 800 mg/day, may be associated with reduced risks of total mortality and mortality due to cardiovascular diseases and cancer. It is worth noting at borderline significance, high Ca intake was associated with a reduced risk of death due to colorectal cancer while Mg intake was associated with an increased risk of gastric cancer mortality, particularly among those with Ca/Mg ratio ≤1.7 (*P* for interaction, 0.05). Analyses limited to those who did not use Ca or multivitamin supplements generated similar results (Data not shown).

We have also conducted stratified analyses to examine whether Ca intake directly interacted with Mg intake in relation to risk of total mortality, mortality due to cardiovascular diseases (coronary heart diseases and stroke) and cancer. For both men and women, we found Mg intake was associated with a significantly increased risk of total mortality among those with Ca intake equal to or below median, but was associated with a significantly reduced risk among those with Ca intake above the median (**Table 5**). Among men Ca intake was associated with a reduced risk of total mortality when Mg intake was above the median while Ca intake was not significantly associated with the risk among those with Mg intake below the median. Similar findings were observed for women although none of the association was statistically significant. These findings indicate a pattern for interactions between Ca and Mg. However, Ca-Mg interactions were not statistically significant for total mortality (Table 5), and mortality due to cardiovascular diseases

(coronary heart diseases and stoke) and cancer and its subtypes in both SWHS and SMHS (Data not shown).

## DISCUSSION

### Statement of principal findings

In contrast to studies conducted in the US with a high Ca/Mg ratio which generally found inverse associations, we found in Chinese populations with a low Ca/Mg intake ratio that high intake of Mg (≥320 mg/day for women and ≥420 mg/day for men) was overall related to an increased risk of total mortality among both men and women, mortality due to cardiovascular diseases among women and mortality due to cancer among men after mutually adjusting for intake of Ca and other confounding factors. Furthermore, we found that Ca/Mg ratio significantly modified the associations between intakes of Ca and Mg with risk of total mortality and coronary heart diseases and possibly cancer whereas we did not identify any significant interactions between Ca and Mg in relation to these outcomes. Among those with Ca/Mg ratios above the median, intakes of Ca and Mg were associated with reduced risks of total mortality, and mortality due to coronary heart diseases for both men and women, and cancer for men while Mg intake was associated with a decreased risk of cancer mortality for women. Conversely, among those with Ca/Mg ratio equal to or below the median, intake of Mg was associated with increased risks of total mortality and mortality due to cardiovascular diseases for men and women as well as colorectal cancer for women and possibly gastric cancer for men.

### Hypothesis and overall biological mechanism

Ionized Ca has a central role in cellular signaling [39], controlling numerous cellular processes [40], while ionized Mg is essential in over 300 biological activities[8]. Ca and Mg have similar chemical properties and share the same homeostatic regulating system including gut absorption and kidney reabsorption to maintain a normal balance of Ca and Mg[1]. Furthermore, the changes in blood or colon lumen concentrations for $Ca^{2+}$ and $Mg^{2+}$ are monitored by the same receptor, the calcium-sensing receptor (CaSR) [1]. Once the Ca or Mg concentration is high, CaSR could respond to it even if the concentration of Mg or Ca, respectively, is low, resulting in the simultaneous depression of the (re)absorption process for both Ca and Mg[2;4]. Thus, in clinics, hypomagnesemia is commonly linked to secondary hypocalciuria[41]. Previous studies also showed that changes in the dietary Ca/Mg balance affected systemic inflammation responses in animal models [3;14]. In addition to inflammation, $Mg^{2+}$ and $Ca^{2+}$ potentially antagonize each other in many other physiologic activities, such as oxidative stress[42] and insulin resistance [18;43], DNA repair, cell differentiation and proliferation, apoptosis, and angiogenesis [3;6;44], which may also be involved in development of cancer, cardiovascular diseases and many other diseases. As we mentioned in the introduction, if the total absorbed number of Ca and Mg ions is relatively constant, the absorbed numbers of Ca and Mg are dependent on Ca/Mg ratio in the gut. Therefore, the Ca/Mg ratio to which gut epithelial cells are directly exposed may modify absorption of Ca and Mg and other activities in gut[10;11].

**Comparison with previous studies**

*Possible explanations on findings with colorectal cancer:* In 2007, we reported from a study conducted in US that Mg intake from dietary source was only related to a non-significantly reduced risk of colorectal adenoma while total Mg intake from both dietary and supplemental

source was associated with a significantly reduced risk [10]. The inverse associations with both total intakes of Ca or Mg may primarily appear among those with Ca/Mg ratio was below 2.78 [10]. Similar to our finding, in a very recent case-control study conducted in Netherlands, Wark et al. found dietary Mg only (not including Mg from supplementation) was marginally significantly related to a reduced risk of colorectal adenoma[45]. In our 2007 report, we found the p for interaction between total Mg and total Ca/Mg ratio was 0.10[10] whereas p for interaction was 0.65 between dietary Mg and dietary Ca/Mg ratio. Interestingly, the study conducted by Wark et al. also did not find a significant interaction between dietary Mg and dietary Ca/Mg ratio (p for interaction=0.86)[45]. It is possible that misclassification in the analyses due to only using Ca and Mg from dietary source may bias the result to the null. In a recent paper based on the analysis of a large clinical trial, Ca supplementation reduced risk of colorectal adenoma recurrence only among those with baseline dietary Ca/Mg ratio less than or equal to 2.63[10;11]. Moreover, the effect of Ca treatment did not significantly differ by baseline intake of Ca or Mg alone[11;46]. Zhang et al found in the Nurses' Health Study, the interaction between total Ca and Mg intakes (p for interaction, 0.17) was also not statistically significant in relation to risk of colorectal cancer incidence[47].

*Overall interpretations for findings on diseases other than colorectal cancer:* Consistent with these published findings on colorectal neoplasia, we found in the current study that the associations between Ca or Mg with total mortality and mortality due to cardiovascular diseases and cancer were not significantly modified by Mg or Ca, respectively, but many of these associations were significantly modified by Ca/Mg ratio. In a recent study, we found high serum Ca/Mg ratio was statistically associated with an increased risk of high-grade prostate

cancer even after adjusting for both serum Ca and Mg[12], indicating that the balance between Ca and Mg may affect risk or pathogenesis of diseases other than colorectal cancer or adenoma. In addition to competition for absorption, a previous study found that Mg supplementation increased urinary Ca excretion if intake of Ca was <800 mg/day[29], suggesting that Mg may suppress Ca reabsorption when Ca/Mg intake ratio is very low. It is possible that the Ca and Mg statuses in the body and specific organs or tissues could be indirectly modified by the dietary Ca/Mg ratio through affecting both absorption and reabsorption processes [29;48]. As a result, it is not surprising that we found the dietary Ca/Mg ratio also modified the effects of Ca and Mg on risk of diseases occurring in organs which do not directly expose to dietary Ca and Mg. However, it is conceivable through the homeostasis regulation by (re)absorption, the Ca/Mg ratio in the gut differs from that in circulation and other systems. Thus, the modification effects of dietary Ca/Mg ratio may become weaker on diseases occurring in organs other than the digestive tract. For example, among women with Ca/Mg ratio ≤ 1.7, high intake of Mg was associated with a 24% of increased risk of total mortality and 66% increased of coronary heart disease death compared to 120% increased risk for colorectal cancer death. Among women with Ca/Mg >1.7, intake of Ca has the strongest inverse association with gastrointestinal cancer.

*Comparison with studies on association of Mg with CVD:* The associations between Mg intake with risk of stroke [49;50] and coronary heart disease [49;51]incidence and death have not been entirely consistent in previous prospective studies. Two meta-analyses found that Mg intake was related to a significantly reduced risk of stroke [49;50]. However, the inverse association was weak and only existed with ischemic stroke, but not hemorrhagic stroke [50]. Also, a previous meta-analysis found Mg intake was non-significantly inversely associated with coronary heart disease[49]. No

study has examined the possible effect modifications by the Ca/Mg ratio. A very recent report from the JACC study conducted in Japan, a population also with a low Ca/Mg ratio, found that dietary intake of Mg was significantly related to reduced risks of mortality due to hemorrhagic stroke in men and cardiovascular diseases in women [51]. However, after adjusting for intakes of Ca and potassium, all these inverse associations not only disappeared, but further became positive associations, which were significant for total stroke in women with an HR (95% CI) of 1.81(1.12-2.94) for the highest quintile intake vs. the lowest (*P* for trend, 0.015) and of borderline significance for ischemic stroke in women (*P* for trend, 0.081). Thus, these findings from the study conducted in a Japanese population are consistent with what we found in Chinese populations. Furthermore, previous cohort studies have relatively consistently found high dietary intake of Mg was associated with a reduced risk of metabolic syndrome [15] and type II diabetes [16-18] and insulin resistance [13] in Western populations. However, clinical trials using different high doses of Mg supplementations led to inconsistent results on glycaemic control among diabetes patients[52]. The null effect in many of these trials could be due to a high dose of Mg supplementation resulting in a very low Ca/Mg ratio (<1.7). Future studies are needed to confirm this possibility.

*Comparison with studies on association of Ca with CVD:* Similar to Mg, previous cohort studies have also provided inconsistent results on the associations between Ca intake and supplemental use of Ca and risk of cardiovascular diseases[53;54]. Meta-analysis of these studies showed a non-significant result with either coronary heart disease or stroke [53]. No study has examined whether the Ca/Mg ratio modifies the association between Ca intake and risk of cardiovascular disease incidence or death. A recent study conducted among a population with a high intake level of

Mg found intake of Ca, but not Mg, to be associated with a reduced risk of total mortality and, likely, mortality due to cardiovascular diseases [54]. In joint analysis, intake of Ca was significantly related to a reduced risk of total mortality only when intake of Mg was under 480 mg/day. It is very important to mention that this study was conducted in a population located in the northern latitude where sunlight is very limited for vitamin D synthesis from autumn to spring [55]. Furthermore, the investigators excluded those who took dietary supplements including vitamin D supplements from the study. As a result, the average intake level of vitamin D was as low as 6.5 µg / day. Thus, it is expected in a population at high risk of vitamin D deficiency that Ca intake would be related to a reduced risk of total mortality even at a very high level, particularly among those with relatively low intake of Mg (no absorption competition from Mg). In contrast, although still controversial, recent findings from reanalysis of the Women's Health Initiative study and meta-analysis of secondary clinical trials data conducted among populations with high Ca/Mg ratio suggest that high Ca supplementation with or without vitamin D may modestly increase the risk of cardiovascular events, especially myocardial infarction[56;57]. Also, we found Ca intake levels between 600-800 mg/day, but not higher than 800 mg/day, may be associated with reduced risks of total mortality and mortality due to cardiovascular diseases and cancer. Our finding is supported by the results from both the Nurses' Health Study and the Health Professionals Follow-up Study. In these two studies, the furthest reduction in risk of colorectal cancer associated with intake of Ca was achieved by intakes of 700-800 mg/day, but no additional reduction in risk was observed at higher intakes of Ca [58].

In additional analysis in the JACC, the reduction in risk of mortality due to coronary heart disease was only significant among those with both high intakes of Ca and Mg compared to

those with both low intakes[51]. This finding indicates that high Ca plus high Mg, not high Ca or Mg alone was significantly associated with a reduced risk. The Ca/Mg ratio for people who had both high Ca and high Mg intakes or those with both low Ca and low Mg intakes is in the middle range (i.e. smaller than those with a high Ca and a low Mg intake, but greater than those with a low Ca and a high Mg intake). Among those with a Ca/Mg ratio in the middle, high intakes of Ca and Mg had a reduced risk compared to those with low intakes of Ca and Mg. Thus, this joint association between Ca with Mg found in the JACC is in general consistent with the modifying effects by Ca/Mg ratio observed in the current study. We have also replicated this joint analysis in the current study and found a similar finding among men, but not women. Also, in the current study, we found many significant interactions between Ca/Mg ratio with Ca or Mg, but zero significant interactions between Ca and Mg intakes in relation to disease mortality, suggesting Ca/Mg ratio has a stronger modifying effect than Ca or Mg alone. The fact is also consistent with that predicted mathematically.

*Possible interpretations on the sex modification:* In the current study of a population with a low dietary Ca/Mg ratio, we found Mg intake (≥320 mg/day) among women and a higher dose among men (i.e. Mg intake ≥420 mg/day) was related to an increased risk of total mortality. Furthermore, we found the associations between intakes of Ca and Mg and risk of total mortality and mortality due to cardiovascular diseases significantly differed by sex. These findings are biologically meaningful because of the effects of estrogen on Mg and Ca metabolism [59]. For example, estrogen shifted Mg from circulation (serum) into cells and, thus, lower Mg intake was required for young women than young men to keep positive magnesium balance[59]. Seelig proposed that the increase of the Ca/Mg intake ratio from 2.0 in 1920s to over 3.0 in the US

contributed to a sharp rise in incidence of cardiovascular diseases in men, but not women[59] and this ratio is continuously rising in recent years[60]. Some previous cohort studies conducted in populations with high Ca/Mg ratio have also provided some support. For example, the Atherosclerosis Risk in Communities study found an inverse association between Mg intake and serum Mg and risk of coronary heart disease in men, but not in women and *P* for interaction was 0.07 for serum Mg with sex [61]. Although a meta-analysis association for cohort studies was not significant, all studies conducted among men had an RR/HR under 1.00 for the association between Mg intake and risk of coronary heart disease while only two studies conducted among women had an RR/HR above 1.00[49]. Mg was weakly, but significantly associated with a reduced risk of stroke in a very recent meta-analysis[50]. However, Health Professionals' Follow-up Study found an inverse association between Mg intake and risk of stroke, particularly among men with hypertension, whereas Mg intake was not related to risk among Nurses' Health Study[49]. Further studies are necessary to understand the potential sex modifications.

*Interesting preliminary observations on gastric cancer and stroke:* One interesting, but preliminary, observation in the current study is that Mg intake may be associated with an increased risk of deaths due to stroke and gastric cancer (among men). Previous studies found that compared to the world average, the Chinese population had a much lower incidence and mortality rate of coronary diseases, but a much higher incidence and mortality rate of stroke; [62] and China is also among the regions with the highest rate of gastric cancer, particularly among men[63]. It is possible that the low Ca/Mg ratio in Chinese populations may partially contribute to the higher risks. However, further studies are necessary to explore this possibility.

**Strengths and weaknesses**

The strengths include a population-based prospective design, large sample size, and high rates for baseline participation and follow-up, which minimize potential differential recall bias or selection bias. The current study has been conducted in a population with a low Ca/Mg intake ratio. Thus, caution should be used to generalize our findings to populations with a high Ca/Mg ratio before further studies have been conducted to examine whether Ca/Mg ratio or Mg and Ca modifies the associations of Ca and Mg intakes with risk of non-gastrointestinal diseases [10;11] in populations with a high Ca/Mg ratio. We have adjusted for many potential confounding factors, including Ca supplement and multivitamin use, and also found similar results in sensitivity analysis by excluding those who used Ca or multivitamin supplements. However, the Ca and Mg contents of drinking water could not be calculated. This may lead to non-differential misclassification of Ca and Mg intake, which usually biases associations toward the null. Finally, sample size became smaller in the analyses by cancer subtype, particularly among men. Thus, some of the null associations in subtype analysis could be due to a small sample.

**Conclusion and clinical and public health implications**

In the current study conducted in populations with lower Ca/Mg ratios, we found that when the Ca/Mg ratio was above 1.7, high intake of Ca was related to a reduced risk of colorectal cancer death and the reduction in risk was the strongest among all the associations between Ca and disease mortality. Conversely, among those with Ca/Mg ratio less than or equal to 1.7, high intake of Mg was related to a significantly increased risk of mortality due to colorectal cancer in women. Collectively, the findings from the current study as well as some previous studies conducted in populations with high Ca/Mg ratios [10;11] indicate that a Ca/Mg ratio between 1.70

and 2.63 may be required for high intakes of Ca and Mg to be protective against colorectal cancer.

In addition to colorectal cancer, the potential modifications by the dietary Ca/Mg ratio and sex may provide possible explanations for the inconsistencies on the associations between intake of Ca and Mg with risk of coronary heart diseases[49;53;54], stroke[49;50;53] and total cancer [54;64] in previous studies.

Future studies are necessary to confirm our finding of modifying effects of the Ca/Mg ratio and to define the optimal Ca/Mg intake ratio range. Our findings, if confirmed, will have a very important public health significance, including selecting optimal doses in the intervention trials and in the prevention strategy development for many common diseases. Furthermore, Ca/Mg ratio should be taken into account when the new RDA or DRI levels of Ca and Mg are developed. For example, lower RDA or DRI levels of Mg for men and women may be required for Chinese populations because they have a low Ca/Mg intake ratio.

**Contributors:** DQ developed the hypothesis and drafted manuscript, and had primary responsibility for final content; WZ, XOS, and WHC designed, directed and obtained funding for the parent studies, and contributed to revisions, and data interpretation of the paper; XD and HC contributed to the data analysis, manuscript revisions, and data interpretation; GY, YTG, YBX, and HL contributed to the study design, data collection of the parent studies, manuscript revisions, and data interpretation; MJS and BJ contributed to the manuscript revisions, and data interpretation of the paper.

**Source of funding:** This study was supported by USPHS grant R37CA70867 and R01CA082729 from the National Institutes of Health. Part of Dr. Dai's effort on the study has been supported by R37CA70867, R01CA082729, R01 AT004660 and R01 CA149633 from National Cancer Institute, Department of Health and Human Services and AICR #08A074-REV from the American Institute for Cancer Research.

The funding sponsor had no role in study design, data collection, statistical analysis and result interpretation, the writing of the report, and the decision to submit for publication. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

**Study approval:** Institutional review board

**Competing interests:** None

**Data sharing**: No additional data available.

## ACKNOWLEDGMENTS

The authors would like to thank the participants and staff for the SWHS and SMHS. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## REFERENCE

(1) Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* 2001; 81(1):239-297.

(2) Hardwick LL, Jones MR, Brautbar N, et al. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. *J Nutr* 1991; 121(1):13-23.

(3) Bussiere FI, Gueux E, Rock E, et al. Protective effect of calcium deficiency on the inflammatory response in magnesium-deficient rats. *Eur J Nutr* 2002; 41(5):197-202.

(4) Norman DA, Fordtran JS, Brinkley LJ, et al. Jejunal and ileal adaptation to alterations in dietary calcium: changes in calcium and magnesium absorption and pathogenetic role of parathyroid hormone and 1,25-dihydroxyvitamin D. *J Clin Invest* 1981; 67(6):1599-1603.

(5) Nielsen FH, Milne DB, Gallagher S, et al. Moderate magnesium deprivation results in calcium retention and altered potassium and phosphorus excretion by postmenopausal women. *Magnes Res* 2007; 20(1):19-31.

(6) Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J* 1984; 108(1):188-193.

(7) SEELIG MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. *Magnes Res* 1990; 3(3):197-215.

(8) Flatman PW. Mechanisms of magnesium transport. *Annu Rev Physiol* 1991; 53:259-271.

(9) Hoenderop JG, Bindels RJ. Epithelial Ca2+ and Mg2+ channels in health and disease. *J Am Soc Nephrol* 2005; 16(1):15-26.

(10) Dai Q, Shrubsole MJ, Ness RM, et al. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007; 86(3):743-751.

(11) Dai Q, Sandler RS, Barry EL, et al. Calcium, Magnesium, and Colorectal Adenoma Recurrence: Results from a Randomized Trial . Epidemiology. In press 2012.

(12) Dai Q, Motley SS, Smith JA, Jr., et al. Blood magnesium, and the interaction with calcium, on the risk of high-grade prostate cancer. *PLoS One* 2011; 6(4):e18237.

(13) Manolio TA, Savage PJ, Burke GL, Hilner JE, Liu K, Orchard TJ et al. Correlates of fasting insulin levels in young adults: the CARDIA study. *J Clin Epidemiol* 1991; 44(6):571-578.

(14) Ziegler D. Type 2 diabetes as an inflammatory cardiovascular disorder. *Curr Mol Med* 2005; 5(3):309-322.

(15) He K, Liu K, Daviglus ML, et al. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; 113(13):1675-1682.

(16) Colditz GA, Manson JE, Stampfer MJ, et al. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 1992; 55(5):1018-1023.

(17) Lopez-Ridaura R, Willett WC, Rimm EB, et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004; 27(1):134-140.

(18) Song Y, Manson JE, Buring JE, et al. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27(1):59-65.

(19) Singh RB. Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnes Trace Elem* 1990; 9(3):143-151.

(20) Al Delaimy WK, Rimm EB, Willett WC, et al. Magnesium intake and risk of coronary heart disease among men. *J Am Coll Nutr* 2004; 23(1):63-70.

(21) Dong JY, Xun P, He K, et al. Magnesium Intake and Risk of Type 2 Diabetes: Meta-analysis of prospective cohort studies. *Diabetes Care* 2011; 34(9):2116-2122.

(22) Larsson SC, Bergkvist L, Wolk A. Magnesium intake in relation to risk of colorectal cancer in women. *JAMA* 2005; 293(1):86-89.

(23) Folsom AR, Hong CP. Magnesium intake and reduced risk of colon cancer in a prospective study of women. *Am J Epidemiol* 2006; 163(3):232-235.

(24) van den Brandt PA, Smits KM, Goldbohm RA, et al. Magnesium intake and colorectal cancer risk in the Netherlands Cohort Study. *Br J Cancer* 2007; 96(3):510-513.

(25) Cai H, Shu XO, Hebert JR, et al. Variation in nutrient intakes among women in Shanghai, China. *Eur J Clin Nutr* 2004; 58(12):1604-1611.

(26) Cai H, Yang G, Xiang YB, et al. Sources of variation in nutrient intakes among men in Shanghai, China. *Public Health Nutr* 2005; 8(8):1293-1299.

(27) Ervin RB, Wang CY, Wright JD, et al. Dietary intake of selected minerals for the United States population: 1999-2000. *Adv Data* 2004;(341):1-5.

(28) SEELIG MS. THE REQUIREMENT OF MAGNESIUM BY THE NORMAL ADULT. SUMMARY AND ANALYSIS OF PUBLISHED DATA. *Am J Clin Nutr* 1964; 14:242-290.

(29) Spencer H, Fuller H, Norris C, et al. Effect of magnesium on the intestinal absorption of calcium in man. *J Am Coll Nutr* 1994; 13(5):485-492.

(30) Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol* 2005; 162(11):1123-1131.

(31) Cai H, Shu XO, Gao YT, et al. A prospective study of dietary patterns and mortality in Chinese women. *Epidemiology* 2007; 18(3):393-401.

(32) Dai Q, Shu XO, Li H, et al. Is green tea drinking associated with a later onset of breast cancer? *Ann Epidemiol* 2010; 20(1):74-81.

(33) Zhang X, Shu XO, Xiang YB, et al. Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. *Am J Clin Nutr* 2011; 94(1):240-246.

(34) Rao C, Yang G, Hu J, et al. Validation of cause-of-death statistics in urban China. *Int J Epidemiol* 2007; 36(3):642-651.

(35) Villegas R, Yang G, Liu D, et al. Validity and reproducibility of the food-frequency questionnaire used in the Shanghai men's health study. *Br J Nutr* 2007; 97(5):993-1000.

(36) Shu XO, Yang G, Jin F, et al. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. *Eur J Clin Nutr* 2003; 58(1):17-23.

(37) Hosmer DW, Lemeshow S. Applied survival analysis. Regression modeling of time to even data. New York: Wiley; 1999.

(38) Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997; 145(1):72-80.

(39) Berridge MJ, Bootman MD, Lipp P. Calcium--a life and death signal. *Nature* 1998; 395(6703):645-648.

(40) Bootman MD, Berridge MJ. The elemental principles of calcium signaling. *Cell* 1995; 83(5):675-678.

(41) Schlingmann KP, Konrad M, Seyberth HW. Genetics of hereditary disorders of magnesium homeostasis. *Pediatr Nephrol* 2004; 19(1):13-25.

(42) Hans CP, Chaudhary DP, Bansal DD. Effect of magnesium supplementation on oxidative stress in alloxanic diabetic rats. *Magnes Res* 2003; 16(1):13-19.

(43) Paolisso G, Sgambato S, Gambardella A, et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992; 55(6):1161-1167.

(44) Wolf FI, Maier JA, Nasulewicz A, et al. Magnesium and neoplasia: From carcinogenesis to tumor growth and progression or treatment. *Arch Biochem Biophys* 2006.

(45) Wark PA, Lau R, Norat T, et al. Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis. *Am J Clin Nutr* 2012.

(46) Wallace K, Baron JA, Cole BF, et al. Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; 96(12):921-925.

(47) Zhang X, Giovannucci EL, Wu K, et al. Magnesium intake, plasma C-peptide, and colorectal cancer incidence in US women: a 28-year follow-up study. *Br J Cancer* 2012; 106(7):1335-1341.

(48) Sahota O, Mundey MK, San P, et al. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int* 2006; 17(7):1013-1021.

(49) Song Y, Manson JE, Cook NR, et al. Dietary magnesium intake and risk of cardiovascular disease among women. *Am J Cardiol* 2005; 96(8):1135-1141.

(50) Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *Am J Clin Nutr* 2012; 95(2):362-366.

(51) Zhang W, Iso H, Ohira T, et al, Tamakoshi A. Associations of dietary magnesium intake with mortality from cardiovascular disease: The JACC study. *Atherosclerosis* 2012.

(52) Song Y, He K, Levitan EB, et al. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med* 2006; 23(10):1050-1056.

(53) Wang L, Manson JE, Sesso HD. Calcium Intake and Risk of Cardiovascular Disease: A Review of Prospective Studies and Randomized Clinical Trials. *Am J Cardiovasc Drugs* 2012.

(54) Kaluza J, Orsini N, Levitan EB, et al. Dietary calcium and magnesium intake and mortality: a prospective study of men. *Am J Epidemiol* 2010; 171(7):801-807.

(55) Steingrimsdottir L, Gunnarsson O, Indridason OS, et al. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. *JAMA* 2005; 294(18):2336-2341.

(56) Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011; 342:d2040.

(57) Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; 341:c3691.

(58) Giovannucci E. Diet, body weight, and colorectal cancer: a summary of the epidemiologic evidence. *J Womens Health (Larchmt )* 2003; 12(2):173-182.

(59) SEELIG MS, Altura BM, Altura BT. Benefits and risks of sex hormone replacement in postmenopausal women. *J Am Coll Nutr* 2004; 23(5):482S-496S.

(60) Rosanoff A. Rising Ca:Mg intake ratio from food in USA Adults: a concern? *Magnes Res* 2010; 23(4):S181-S193.

(61) Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 1998; 136(3):480-490.

(62) Wu Z, Yao C, Zhao D, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. *Circulation* 2001; 103(3):462-468.

(63) Parkin DM, Whelen SL, Ferlay J, et al. Cancer Incidence in Five Continents. [7]. 1997. Lyon, International Agency for Research on Cancer.

(64) Li K, Kaaks R, Linseisen J, et al. Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg). *Cancer Causes Control* 2011.

**Table 1. Baseline Lifestyle Factors and Demographics by Intakes of calcium and magnesium, the Shanghai Women's Health Study(SWHS) and the Shanghai Men Health Study (SMHS), 1996-2009**

| | Calcium (mg/day) | | | Magnesium (mg/day) | | |
|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | <251 | 251-<320 | ≥320 |
| **Shanghai Women's Health Study** | | | | | | |
| **Married, %** | 87.87 | 90.28 | 88.45 | 87.93 | 89.87 | 88.96 |
| **Smokers, %** | 3.64 | 2.13 | 2.07 | 3.41 | 2.18 | 2.5 |
| **Alcohol drinkers, %** | 2.08 | 2.17 | 2.7 | 2.11 | 2.08 | 2.7 |
| **Tea drinker, %** | 24.84 | 32.23 | 36.22 | 26.09 | 31.4 | 34.24 |
| **Ginseng use, %** | 25.01 | 30.35 | 34.85 | 26.75 | 29.94 | 31.55 |
| **Ca Supplement use, %** | 15.41 | 20.33 | 25.09 | 17.49 | 19.75 | 21.43 |
| **Multivitamin use, %** | 3.98 | 8.1 | 11.68 | 5.74 | 7.52 | 8.77 |
| **Physically active, %** | 30.12 | 36.06 | 43.32 | 31.78 | 35.64 | 39.79 |
| **High school or up , %** | 8.75 | 15.55 | 19.78 | 10.82 | 15.2 | 15.77 |
| **Age (years), mean (SD)** | 53.37(9.45) | 51.88(8.79) | 51.85(8.54) | 53.48(9.55) | 51.95(8.74) | 51.68(8.45) |
| **BMI(kg/m2), mean (SD)** | 24.18(3.53) | 23.83(3.36) | 23.96(3.28) | 23.85(3.46) | 24.00(3.38) | 24.29(3.40) |
| **Daily nutrient intake adjusted for age and total energy, except for total energy** | | | | | | |
| **Total energy** [a] | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) |
| **Saturated fat** | 7.02(0.02) | 8.99(0.02) | 10.99(0.03) | 7.89(0.02) | 8.62(0.02) | 9.65(0.03) |
| **Fiber** | 9.55(0.02) | 11.15(0.02) | 13.51(0.03) | 8.26(0.02) | 11.17(0.02) | 15.26(0.03) |
| **Phosphorus** | 852.77(0.63) | 985.46(0.66) | 1162.48(0.91) | 843.66(0.85) | 975.56(0.77) | 1161.18(1.16) |
| **Calcium** | 310.97(0.54) | 493.36(0.57) | 726.90(0.78) | 335.37(0.99) | 476.36(0.90) | 668.24(1.34) |
| **Magnesium** | 246.51(0.21) | 279.27(0.22) | 329.68(0.30) | 231.88(0.23) | 278.50(0.21) | 347.30(0.31) |
| **Retinol** | 146.88(0.95) | 186.49(1.00) | 228.98(1.37) | 163.43(1.14) | 178.50(1.03) | 203.98(1.55) |
| **Vitamin E** | 10.72(0.02) | 13.68(0.03) | 18.63(0.03) | 9.87(0.03) | 13.61(0.03) | 19.39(0.04) |
| **Folate** | 254.15(0.43) | 295.56(0.45) | 356.16(0.62) | 227.05(0.47) | 296.25(0.43) | 391.14(0.64) |
| **Sodium** | 252.92(0.52) | 355.20(0.55) | 489.11(0.75) | 260.13(0.73) | 345.16(0.67) | 467.53(1.00) |
| **Potassium** | 1479.84(2.17) | 1826.56(2.28) | 2293.21(3.14) | 1360.48(2.48) | 1808.59(2.25) | 2440.75(3.38) |
| **Zinc** | 10.20(0.01) | 10.85(0.01) | 11.84(0.01) | 10.02(0.01) | 10.83(0.01) | 12.02(0.01) |
| **Shanghai Men's Health Study** | | | | | | |
| **Married, %** | 96.37 | 97.37 | 97.70 | 96.48 | 97.44 | 97.57 |
| **Smokers, %** | 76.18 | 70.32 | 65.45 | 72.67 | 69.22 | 68.34 |
| **Alcohol drinkers, %** | 35.66 | 33.56 | 32.74 | 37.01 | 32.52 | 32.88 |
| **Tea drinker, %** | 64.96 | 66.92 | 68.45 | 64.3 | 67.47 | 68.3 |
| **Ginseng use, %** | 26.27 | 30.99 | 36.7 | 29.24 | 31.99 | 34.14 |
| **Ca Supplement use, %** | 3.07 | 4.36 | 5.91 | 4.02 | 4.67 | 5.11 |
| **Multivitamin use, %** | 3.92 | 6.92 | 10.04 | 6.00 | 7.58 | 8.32 |
| **Physically active, %** | 28.03 | 33.68 | 41.16 | 31.45 | 34.69 | 38.28 |
| **High school or up, %** | 14.39 | 22.37 | 29.02 | 19.14 | 23.91 | 25.07 |
| **Age (years), mean (SD)** [b] | 55.90(10.27) | 55.28(9.73) | 55.17(9.43) | 56.91(10.58) | 55.56(9.70) | 54.46(9.20) |
| **BMI(kg/m2), mean (SD)** [b] | 23.47(3.18) | 23.67(3.09) | 23.90(3.00) | 23.25(3.16) | 23.64(3.04) | 24.02(3.03) |
| **Daily nutrient intake adjusted for age and total energy, except for total energy** | | | | | | |
| **Total energy** [a] | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) |
| **Saturated fat** | 8.16(0.03) | 9.74(0.03) | 11.85(0.03) | 9.59(0.04) | 9.92(0.03) | 10.88(0.03) |
| **Fiber** | 9.27(0.03) | 10.72(0.02) | 13.28(0.02) | 8.17(0.03) | 10.32(0.02) | 14.02(0.02) |
| **Phosphorus** | 956.75(1.17) | 1081.00(0.93) | 1271.73(0.87) | 953.79(1.56) | 1071.31(1.08) | 1270.89(1.11) |
| **Calcium** | 340.34(1.12) | 512.58(0.89) | 778.31(0.83) | 379.76(1.83) | 518.93(1.27) | 740.23(1.30) |
| **Magnesium** | 271.18(0.37) | 303.34(0.30) | 359.14(0.28) | 258.30(0.45) | 297.74(0.31) | 367.15(0.32) |
| **Retinol** | 120.06(1.17) | 154.78(0.93) | 198.50(0.87) | 142.50(1.41) | 156.14(0.98) | 183.74(1.00) |
| **Vitamin E** | 10.72(0.04) | 13.48(0.03) | 18.43(0.03) | 10.13(0.05) | 13.15(0.03) | 18.73(0.04) |
| **Folate** | 271.83(0.75) | 319.26(0.60) | 398.67(0.56) | 245.92(0.87) | 308.91(0.61) | 415.67(0.62) |
| **Sodium** | 250.29(0.92) | 345.02(0.73) | 489.36(0.68) | 271.89(1.28) | 345.24(0.89) | 470.94(0.91) |
| **Potassium** | 1464.92(3.41) | 1778.86(2.70) | 2289.70(2.53) | 1399.54(4.28) | 1739.67(2.97) | 2326.91(3.04) |
| **Zinc** | 11.54(0.01) | 12.23(0.01) | 13.40(0.01) | 11.38(0.01) | 12.13(0.01) | 13.50(0.01) |

[a] adjusted for age only. [b] SD, standard deviation.

**Table 2 Hazard Ratios (HRs) and 95% Confidence Intervals (95% CIs) for Total Mortality, and Mortality due to Cardiovascular Diseases and Cancer by Tertiles of Calcium and Magnesium among women in Shanghai**

| | Calcium intake (mg/day) | | | | | Magnesium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | P for trend | P for interaction | <251 | 251-<320 | ≥320 | P for trend | P for interaction |
| Person years | 349874.66 | 281646.47 | 175026.49 | | | 335378.89 | 271235.72 | 199933.00 | | |
| **Total Mortality** | | | | | | | | | | |
| Cases | 2019 | 1155 | 632 | | | 1992 | 1108 | 706 | | |
| Model 1 | 1.00 | 1.04(0.95,1.15) | 1.06(0.92,1.22) | 0.39 | | 1.00 | 1.04(0.94,1.16) | 1.09(0.94,1.27) | 0.27 | |
| Model 2 | 1.00 | 1.05(0.96,1.16) | 1.08(0.94,1.25) | 0.25 | 0.54 | 1.00 | 1.04(0.94,1.15) | 1.09(0.94,1.27) | 0.27 | 0.07 |
| [a] Ratio≤1.7 | 1.00 | 0.99(0.86,1.13) | 1.03(0.78,1.36) | 0.99 | | 1.00 | 1.14(1.00,1.30) | 1.24(1.02,1.51) | 0.02 | |
| [a] Ratio>1.7 | 1.00 | 1.03(0.85,1.24) | 1.06(0.81,1.39) | 0.68 | | 1.00 | 0.90(0.76,1.06) | 0.88(0.68,1.13) | 0.31 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | |
| Cases | 649 | 321 | 177 | | | 625 | 311 | 211 | | |
| Model 1 | 1.00 | 1.03(0.86,1.22) | 1.08(0.84,1.40) | 0.57 | | 1.00 | 1.11(0.92,1.34) | 1.35(1.03,1.77) | 0.04 | |
| Model 2 | 1.00 | 1.03(0.86,1.22) | 1.08(0.83,1.40) | 0.57 | 0.18 | 1.00 | 1.11(0.92,1.34) | 1.35(1.03,1.77) | 0.04 | 0.09 |
| [a] Ratio≤1.7 | 1.00 | 1.01(0.79,1.30) | 1.21(0.74,1.99) | 0.61 | | 1.00 | 1.17(0.93,1.48) | 1.53(1.08,2.16) | 0.02 | |
| [a] Ratio>1.7 | 1.00 | 0.95(0.67,1.35) | 1.07(0.64,1.79) | 0.69 | | 1.00 | 1.01(0.74,1.39) | 1.14(0.71,1.85) | 0.60 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | |
| Cases | 284 | 148 | 79 | | | 290 | 129 | 92 | | |
| Model 1 | 1.00 | 1.01(0.78,1.31) | 1.01(0.69,1.49) | 0.94 | | 1.00 | 0.96(0.73,1.28) | 1.19(0.79,1.78) | 0.46 | |
| Model 2 | 1.00 | 1.02(0.78,1.32) | 1.04(0.71,1.54) | 0.84 | 0.21 | 1.00 | 0.96(0.73,1.28) | 1.19(0.79,1.79) | 0.46 | 0.02 |
| [a] Ratio≤1.7 | 1.00 | 0.97(0.67,1.42) | 1.92(1.00,3.70) | 0.27 | | 1.00 | 1.01(0.70,1.46) | 1.69(1.02,2.80) | 0.07 | |
| [a] Ratio>1.7 | 1.00 | 0.86(0.53,1.40) | 0.85(0.41,1.76) | 0.68 | | 1.00 | 0.92(0.59,1.45) | 0.86(0.43,1.74) | 0.68 | |
| **Mortality due to Stroke** | | | | | | | | | | |
| Cases | 365 | 173 | 98 | | | 335 | 182 | 119 | | |
| Model 1 | 1.00 | 1.04(0.82,1.32) | 1.13(0.80,1.60) | 0.50 | | 1.00 | 1.25(0.97,1.61) | 1.50(1.03,2.16) | 0.03 | |
| Model 2 | 1.00 | 1.03(0.81,1.31) | 1.11(0.78,1.57) | 0.59 | 0.49 | 1.00 | 1.25(0.97,1.60) | 1.50(1.03,2.17) | 0.03 | 0.81 |
| [a] Ratio≤1.7 | 1.00 | 1.05(0.76,1.44) | 0.72(0.33,1.58) | 0.79 | | 1.00 | 1.30(0.95,1.77) | 1.40(0.87,2.23) | 0.12 | |
| [a] Ratio>1.7 | 1.00 | 1.07(0.65,1.77) | 1.35(0.66,2.77) | 0.34 | | 1.00 | 1.14(0.73,1.78) | 1.46(0.75,2.85) | 0.26 | |
| **Mortality due to all Cancers** | | | | | | | | | | |
| Cases | 789 | 556 | 271 | | | 756 | 537 | 323 | | |
| Model 1 | 1.00 | 1.09(0.95,1.26) | 0.90(0.72,1.12) | 0.51 | | 1.00 | 1.05(0.90,1.23) | 0.89(0.70,1.14) | 0.42 | |
| Model 2 | 1.00 | 1.10(0.95,1.27) | 0.92(0.74,1.15) | 0.68 | 0.24 | 1.00 | 1.05(0.90,1.23) | 0.89(0.70,1.14) | 0.42 | 0.78 |
| [a] Ratio≤1.7 | 1.00 | 1.03(0.85,1.26) | 0.82(0.54,1.25) | 0.73 | | 1.00 | 1.19(0.98,1.46) | 1.13(0.83,1.54) | 0.35 | |
| [a] Ratio>1.7 | 1.00 | 1.28(0.93,1.77) | 0.99(0.64,1.55) | 0.42 | | 1.00 | 0.85(0.66,1.10) | 0.61(0.41,0.92) | 0.02 | |
| **Mortality due to Lung cancer** | | | | | | | | | | |
| Cases | 171 | 109 | 50 | | | 156 | 109 | 65 | | |
| Model 1 | 1.00 | 1.00(0.73,1.37) | 0.76(0.47,1.24) | 0.34 | | 1.00 | 1.14(0.80,1.61) | 1.01(0.59,1.71) | 0.93 | |
| Model 2 | 1.00 | 1.02(0.74,1.40) | 0.81(0.50,1.32) | 0.47 | 0.87 | 1.00 | 1.15(0.81,1.62) | 1.01(0.60,1.72) | 0.92 | 0.95 |
| [a] Ratio≤1.7 | 1.00 | 1.13(0.73,1.76) | 1.78(0.82,3.87) | 0.22 | | 1.00 | 1.45(0.94,2.24) | 1.65(0.87,3.15) | 0.11 | |
| [a] Ratio>1.7 | 1.00 | 0.87(0.42,1.81) | 0.36(0.13,1.02) | 0.01 | | 1.00 | 0.64(0.36,1.13) | 0.30(0.11,0.77) | 0.01 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality due to Colorectal cancer** | | | | | | | | | | |
| Cases | 109 | 76 | 48 | | | 96 | 77 | 60 | | |
| Model 1 | 1.00 | 0.89(0.60,1.30) | 0.76(0.43,1.34) | 0.34 | | 1.00 | 1.19(0.78,1.82) | 1.32(0.70,2.51) | 0.39 | |
| Model 2 | 1.00 | 0.87(0.60,1.28) | 0.73(0.41,1.29) | 0.28 | 0.49 | 1.00 | 1.20(0.79,1.84) | 1.34(0.70,2.54) | 0.37 | 0.19 |
| [a] Ratio≤1.7 | 1.00 | 1.11(0.66,1.86) | 0.63(0.19,2.08) | 0.84 | | 1.00 | 1.92(1.11,3.33) | 2.20(0.96,5.04) | 0.05 | |
| [a] Ratio>1.7 | 1.00 | 0.50(0.23,1.10) | 0.32(0.11,0.94) | 0.05 | | 1.00 | 0.58(0.30,1.13) | 0.56(0.20,1.53) | 0.25 | |
| **Mortality due to Gastric cancer** | | | | | | | | | | |
| Cases | 108 | 68 | 32 | | | 114 | 58 | 36 | | |
| Model 1 | 1.00 | 1.15(0.77,1.72) | 1.05(0.57,1.92) | 0.80 | | 1.00 | 0.83(0.54,1.28) | 0.77(0.40,1.50) | 0.42 | |
| Model 2 | 1.00 | 1.17(0.78,1.75) | 1.09(0.59,2.03) | 0.69 | 0.23 | 1.00 | 0.83(0.54,1.28) | 0.77(0.40,1.50) | 0.42 | 0.33 |
| [a] Ratio≤1.7 | 1.00 | 0.75(0.42,1.35) | 1.34(0.47,3.77) | 0.81 | | 1.00 | 0.65(0.37,1.16) | 0.95(0.42,2.15) | 0.72 | |
| [a] Ratio>1.7 | 1.00 | 3.41(1.30,8.99) | 3.92(1.05,14.68) | 0.10 | | 1.00 | 1.10(0.54,2.23) | 0.63(0.20,2.01) | 0.49 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.

In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[a] Model 2 was used .

**Table 3 Hazard Ratios (HRS) and 95% Confidence Intervals (95% CIs) for Total Mortality, and Mortality due to Cardiovascular Diseases by Tertiles of Calcium and Magnesium among men in Shanghai**

| | Calcium intake (mg/day) | | | | | Magnesium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | p for trend | p for interaction | <251 | 251-<320 | ≥320 | p for trend | p for interaction |
| Person years | 77215.85 | 112600.73 | 147167.01 | | | 74633.02 | 109118.9 | 153231.68 | | |
| **Total Mortality** | | | | | | | | | | |
| Cases | 820 | 798 | 800 | | | 904 | 715 | 799 | | |
| Model 1 | 1.00 | 0.88(0.77,1.01) | 0.79(0.66,0.95) | 0.01 | | 1.00 | 0.80(0.70,0.93) | 0.87(0.70,1.07) | 0.23 | |
| Model 2 | 1.00 | 0.90(0.78,1.02) | 0.82(0.68,0.99) | 0.04 | 0.01 | 1.00 | 0.81(0.70,0.93) | 0.87(0.71,1.07) | 0.23 | 0.19 |
| [a]Ratio≤1.7 | 1.00 | 0.97(0.79,1.18) | 0.95(0.66,1.36) | 0.73 | | 1.00 | 0.98(0.79,1.21) | 1.23(0.90,1.69) | 0.19 | |
| [a]Ratio>1.7 | 1.00 | 0.70(0.56,0.89) | 0.59(0.44,0.80) | 0.00 | | 1.00 | 0.69(0.57,0.84) | 0.66(0.50,0.88) | 0.01 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | |
| Cases | 305 | 273 | 222 | | | 323 | 246 | 231 | | |
| Model 1 | 1.00 | 0.91(0.72,1.14) | 0.72(0.52,0.99) | 0.04 | | 1.00 | 0.87(0.68,1.11) | 0.83(0.58,1.20) | 0.33 | |
| Model 2 | 1.00 | 0.93(0.74,1.16) | 0.75(0.54,1.04) | 0.08 | 0.03 | 1.00 | 0.88(0.68,1.12) | 0.84(0.58,1.21) | 0.35 | 0.07 |
| [a]Ratio≤1.7 | 1.00 | 1.01(0.73,1.40) | 0.92(0.49,1.70) | 0.90 | | 1.00 | 1.17(0.83,1.66) | 1.02(0.60,1.73) | 0.91 | |
| [a]Ratio>1.7 | 1.00 | 0.91(0.59,1.40) | 0.73(0.42,1.29) | 0.19 | | 1.00 | 0.66(0.47,0.94) | 0.66(0.39,1.11) | 0.12 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | |
| Cases | 137 | 143 | 115 | | | 155 | 118 | 122 | | |
| Model 1 | 1.00 | 0.91(0.66,1.26) | 0.63(0.40,1.00) | 0.05 | | 1.00 | 0.69(0.49,0.98) | 0.64(0.38,1.08) | 0.10 | |
| Model 2 | 1.00 | 0.93(0.67,1.29) | 0.66(0.42,1.06) | 0.08 | 0.09 | 1.00 | 0.70(0.49,0.99) | 0.65(0.38,1.09) | 0.11 | 0.54 |
| [a]Ratio≤1.7 | 1.00 | 1.16(0.72,1.86) | 1.64(0.73,3.70) | 0.28 | | 1.00 | 1.01(0.61,1.68) | 0.91(0.42,1.96) | 0.81 | |
| [a]Ratio>1.7 | 1.00 | 0.88(0.47,1.65) | 0.48(0.21,1.09) | 0.02 | | 1.00 | 0.48(0.30,0.78) | 0.43(0.21,0.88) | 0.02 | |
| **Mortality due to Stroke** | | | | | | | | | | |
| Cases | 168 | 130 | 107 | | | 168 | 128 | 109 | | |
| Model 1 | 1.00 | 0.91(0.66,1.24) | 0.81(0.52,1.26) | 0.35 | | 1.00 | 1.08(0.77,1.53) | 1.06(0.63,1.76) | 0.84 | |
| Model 2 | 1.00 | 0.92(0.67,1.27) | 0.85(0.54,1.33) | 0.47 | 0.19 | 1.00 | 1.09(0.77,1.54) | 1.06(0.63,1.77) | 0.83 | 0.06 |
| [a]Ratio≤1.7 | 1.00 | 0.90(0.58,1.41) | 0.42(0.15,1.19) | 0.21 | | 1.00 | 1.32(0.82,2.12) | 1.08(0.52,2.24) | 0.78 | |
| [a]Ratio>1.7 | 1.00 | 0.99(0.54,1.80) | 1.20(0.54,2.65) | 0.52 | | 1.00 | 0.93(0.56,1.54) | 1.02(0.48,2.16) | 0.94 | |
| **Mortality due to all Cancers** | | | | | | | | | | |
| Cases | 320 | 337 | 394 | | | 335 | 316 | 400 | | |
| Model 1 | 1.00 | 0.86(0.70,1.05) | 0.79(0.60,1.04) | 0.10 | | 1.00 | 0.84(0.68,1.04) | 0.93(0.68,1.28) | 0.74 | |
| Model 2 | 1.00 | 0.87(0.71,1.06) | 0.81(0.61,1.07) | 0.14 | 0.23 | 1.00 | 0.84(0.68,1.05) | 0.93(0.68,1.29) | 0.75 | 0.97 |
| Ratio≤1.7 | 1.00 | 0.88(0.65,1.20) | 0.73(0.42,1.27) | 0.26 | | 1.00 | 0.93(0.66,1.30) | 1.31(0.80,2.13) | 0.26 | |
| Ratio>1.7 | 1.00 | 0.68(0.47,0.98) | 0.59(0.37,0.93) | 0.05 | | 1.00 | 0.80(0.60,1.06) | 0.74(0.49,1.14) | 0.19 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.

In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[a] Model 2 was used .

**Table 4 Hazard Ratios (HRS) and 95% Confidence Intervals (95% CIs) for Total Mortality, and Mortality due to Cardiovascular Diseases by Calcium and Magnesium intake among men in Shanghai**

| | Calcium intake (mg/day) | | | | | | Magnesium intake (mg/day) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | 600-<800 | ≥800 | p for trend | p for interaction | <251 | 251-<320 | 320-<420 | ≥420 | p for trend | p for interaction |
| Person years | 77215.85 | 112600.73 | 90733.06 | 56433.95 | | | 74633.02 | 109118.90 | 108337.41 | 44894.27 | | |
| **Total Mortality** | | | | | | | | | | | | |
| Cases | 820 | 798 | 486 | 314 | | | 904 | 715 | 564 | 235 | | |
| Model 1 | 1.00 | 0.93(0.81,1.06) | 0.79(0.66,0.95) | 1.03(0.80,1.31) | 0.50 | | 1.00 | 0.89(0.77,1.04) | 0.96(0.77,1.19) | 1.40(1.02,1.93) | 0.13 | |
| Model 2 | 1.00 | 0.95(0.83,1.09) | 0.83(0.69,1.00) | 1.12(0.87,1.44) | 0.97 | 0.01 | 1.00 | 0.89(0.77,1.04) | 0.96(0.78,1.20) | 1.41(1.02,1.93) | 0.13 | 0.19 |
| [a]Ratio≤1.7 | 1.00 | 0.96(0.79,1.17) | 0.98(0.68,1.40) | 0.70(0.29,1.68) | 0.63 | | 1.00 | 0.99(0.79,1.23) | 1.24(0.90,1.70) | 1.30(0.79,2.13) | 0.14 | |
| [a]Ratio>1.7 | 1.00 | 0.80(0.63,1.02) | 0.69(0.50,0.95) | 0.97(0.64,1.48) | 0.87 | | 1.00 | 0.84(0.68,1.03) | 0.83(0.61,1.13) | 1.39(0.89,2.17) | 0.48 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | | | |
| Cases | 305 | 273 | 135 | 87 | | | 323 | 246 | 168 | 63 | | |
| Model 1 | 1.00 | 0.94(0.75,1.19) | 0.70(0.51,0.97) | 0.91(0.59,1.40) | 0.21 | | 1.00 | 0.93(0.72,1.20) | 0.88(0.61,1.28) | 1.20(0.69,2.08) | 0.95 | |
| Model 2 | 1.00 | 0.97(0.77,1.23) | 0.74(0.53,1.03) | 1.01(0.65,1.57) | 0.42 | 0.03 | 1.00 | 0.94(0.72,1.21) | 0.88(0.61,1.28) | 1.19(0.69,2.07) | 0.94 | 0.07 |
| [a]Ratio≤1.7 | 1.00 | 1.01(0.73,1.40) | 0.93(0.50,1.74) | 0.80(0.18,3.57) | 0.86 | | 1.00 | 1.19(0.84,1.70) | 1.02(0.60,1.74) | 1.18(0.51,2.74) | 0.89 | |
| [a]Ratio>1.7 | 1.00 | 1.05(0.67,1.65) | 0.86(0.48,1.56) | 1.31(0.61,2.82) | 0.70 | | 1.00 | 0.74(0.51,1.08) | 0.75(0.43,1.31) | 1.05(0.46,2.39) | 0.89 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | | | |
| Cases | 137 | 143 | 70 | 45 | | | 155 | 118 | 81 | 41 | | |
| Model 1 | 1.00 | 0.94(0.68,1.31) | 0.63(0.39,1.00) | 0.75(0.41,1.39) | 0.12 | | 1.00 | 0.79(0.54,1.14) | 0.72(0.42,1.23) | 1.18(0.54,2.56) | 0.88 | |
| Model 2 | 1.00 | 0.97(0.70,1.35) | 0.66(0.41,1.06) | 0.83(0.44,1.56) | 0.22 | 0.09 | 1.00 | 0.80(0.55,1.15) | 0.73(0.42,1.24) | 1.18(0.55,2.56) | 0.89 | 0.54 |
| [a]Ratio≤1.7 | 1.00 | 1.15(0.72,1.85) | 1.69(0.75,3.81) | 1.02(0.12,8.52) | 0.33 | | 1.00 | 1.05(0.62,1.77) | 0.92(0.43,2.00) | 1.20(0.37,3.92) | 0.99 | |
| [a]Ratio>1.7 | 1.00 | 0.94(0.49,1.82) | 0.52(0.22,1.20) | 0.63(0.21,1.86) | 0.14 | | 1.00 | 0.59(0.35,1.00) | 0.55(0.25,1.20) | 0.96(0.31,2.95) | 0.67 | |
| **Mortality due to Stroke** | | | | | | | | | | | | |
| Cases | 168 | 130 | 65 | 42 | | | 168 | 128 | 87 | 22 | | |
| Model 1 | 1.00 | 0.95(0.69,1.31) | 0.79(0.50,1.24) | 1.08(0.59,1.98) | 0.80 | | 1.00 | 1.09(0.76,1.56) | 1.06(0.63,1.78) | 1.08(0.48,2.41) | 0.89 | |
| Model 2 | 1.00 | 0.97(0.70,1.35) | 0.83(0.52,1.31) | 1.19(0.64,2.21) | 0.97 | 0.19 | 1.00 | 1.09(0.76,1.57) | 1.06(0.63,1.78) | 1.07(0.48,2.40) | 0.89 | 0.06 |
| [a]Ratio≤1.7 | 1.00 | 0.91(0.58,1.41) | 0.39(0.13,1.20) | 0.65(0.08,5.30) | 0.22 | | 1.00 | 1.31(0.81,2.13) | 1.08(0.52,2.24) | 1.04(0.30,3.57) | 0.92 | |
| [a]Ratio>1.7 | 1.00 | 1.25(0.66,2.34) | 1.57(0.68,3.63) | 2.97(1.00,8.87) | 0.04 | | 1.00 | 0.93(0.54,1.60) | 1.02(0.46,2.25) | 1.02(0.31,3.40) | 0.90 | |
| **Mortality due to all Cancers** | | | | | | | | | | | | |
| Cases | 320 | 337 | 236 | 158 | | | 335 | 316 | 273 | 127 | | |
| Model 1 | 1.00 | 0.90(0.73,1.10) | 0.80(0.60,1.05) | 0.95(0.66,1.38) | 0.55 | | 1.00 | 0.97(0.77,1.23) | 1.10(0.78,1.54) | 1.68(1.03,2.74) | 0.07 | |
| Model 2 | 1.00 | 0.91(0.74,1.12) | 0.82(0.62,1.08) | 1.00(0.68,1.46) | 0.72 | 0.23 | 1.00 | 0.97(0.77,1.23) | 1.10(0.78,1.54) | 1.68(1.03,2.74) | 0.06 | 0.97 |
| [a]Ratio≤1.7 | 1.00 | 0.88(0.65,1.19) | 0.75(0.43,1.31) | 0.51(0.15,1.79) | 0.21 | | 1.00 | 0.93(0.65,1.32) | 1.31(0.80,2.15) | 1.33(0.62,2.84) | 0.22 | |
| [a]Ratio>1.7 | 1.00 | 0.73(0.50,1.08) | 0.65(0.40,1.04) | 0.78(0.42,1.46) | 0.74 | | 1.00 | 1.03(0.74,1.42) | 1.04(0.65,1.66) | 1.91(0.97,3.76) | 0.18 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.
In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.
[a] Model 2 was used .

**Table 5. Hazard Ratios (HRS)[a] and 95% Confidence Intervals (95% CIs) for Total Mortality by tertiles of calcium and magnesium intake among women and men stratified by the median intake of magnesium and calcium, respectively.**

| | | Calcium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|
| | | **<480** | **480-<600** | **≥600** | **p for trend** | **p for interaction** |
| SWHS | All subjects | 1.00 | 1.05(0.96,1.16) | 1.08(0.94,1.25) | 0.25 | 0.42 |
| | [b]Mg≤284.3 | 1.00 | 1.06(0.95,1.19) | 1.19(0.93,1.52) | 0.15 | |
| | [b]Mg>284.3 | 1.00 | 0.84(0.69,1.03) | 0.82(0.64,1.05) | 0.19 | |
| SMHS | All subjects | 1.00 | 0.90(0.78,1.02) | 0.82(0.68,0.99) | 0.04 | 0.11 |
| | [b]Mg≤284.3 | 1.00 | 0.97(0.82,1.14) | 0.91(0.68,1.22) | 0.54 | |
| | [b]Mg>284.3 | 1.00 | 0.88(0.67,1.16) | 0.75(0.54,1.03) | 0.03 | |
| | | **Magnesium intake (mg/day)** | | | | |
| | | **<251** | **251-<320** | **≥320** | **p for trend** | **p for interaction** |
| SWHS | All subjects | 1.00 | 1.04(0.94,1.15) | 1.09(0.94,1.27) | 0.27 | 0.42 |
| | [c]Ca≤491 | 1.00 | 1.12(0.99,1.26) | 1.31(1.05,1.64) | 0.01 | |
| | [c]Ca>491 | 1.00 | 0.79(0.64,0.98) | 0.70(0.52,0.95) | 0.03 | |
| SMHS | All subjects | 1.00 | 0.81(0.70,0.93) | 0.87(0.71,1.07) | 0.23 | 0.11 |
| | [c]Ca≤491 | 1.00 | 1.00(0.82,1.21) | 1.59(1.15,2.20) | 0.06 | |
| | [c]Ca>491 | 1.00 | 0.70(0.55,0.88) | 0.57(0.42,0.79) | 0.00 | |

[a] Model 2 was used. age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted. Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[b] Mg= magnesium intake

[c] Ca= calcium intake

**Original Research Article**

# Dietary Calcium and Magnesium, Calcium/magnesium Ratio, and Mortality: Results from the Shanghai Women's and Men's Health Studies

Qi Dai[1], Xiao-Ou Shu[1], Xinqing Deng[1], Yong-Bing Xiang[2], Honglan Li[2], Gong Yang[1], Martha J Shrubsole[1], Butian Ji[3], Hui Cai [1], Wong-Ho Chow[3,4], Yu-Tang Gao[2], Wei Zheng[1]

[1]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt School of Medicine, Nashville, TN, USA

[2]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[4]Department of Epidemiology, Division of Cancer Prevention and Population Sciences, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Dr. Qi Dai, Vanderbilt Epidemiology Center, Institute for Medicine & Public Health, Sixth Floor, Suite 600, 2525 West End Avenue, Nashville, TN 37203-1738

Phone: 615-936-0707, Fax: 615-936-8290, E-mail: qi.dai@vanderbilt.edu

**Running Title:** calcium/magnesium ratio and mortality

**Key words:** Magnesium, calcium, ratio, mortality, cancer and cardiovascular diseases

## ABSTRACT

**Objectives:** Magnesium (Mg) and calcium (Ca) antagonize each other in (re)absorption, inflammation and many other physiologic activities. Based on mathematical estimation, the absorbed number of Ca or Mg depends on the dietary ratio of Ca to Mg intake. We hypothesize that dietary Ca/Mg ratio modifies the effects of Ca and Mg on mortality due to gastrointestinal tract cancer, and perhaps, mortality due to diseases occurring in other organs or systems.

**Design, Setting, Participants:** We conducted analyses using data from two large population-based cohorts (Shanghai Women's and Men's Health Studies) conducted in China with over 130,000 participants.

**Primary outcome measures:** All-cause mortality and disease-specific mortality

**Results:** In this Chinese population with a low Ca/Mg intake ratio (a median of 1.7 vs. around 3.0 in US populations), intakes of Mg greater than US RDA levels (320mg/day among women and 420mg/day among men) were related to increased risks of total mortality for both women and men. Consistent with our hypothesis, Ca/Mg intake ratio significantly modified the associations of intakes of Ca and Mg with mortality risk whereas no significant interactions between Ca and Mg in relation to outcome were found. The associations differed by gender. Among men with Ca/Mg ratio >1.7, increased intakes of Ca and Mg were associated with reduced risks of total mortality, and mortality due to coronary heart diseases. In the same group, intake of Ca was associated with a reduced risk of mortality due to cancer. Among women with Ca/Mg ratio ≤1.7, intake of Mg was associated with increased risks of total mortality, and mortality due to cardiovascular diseases and colorectal cancer.

**Conclusions:** These results, if confirmed, may help to understand the optimal balance between Ca and Mg in the etiology and prevention of these common diseases and reduction in mortality.

## Article summary

*Article focus*

- Modifying effects of Ca/Mg intake ratio on the associations between intakes of Ca and Mg with disease mortality
- The effect of high Mg intake on disease mortality differs in populations with a very low Ca/Mg intake ratio from those (i.e. Western populations) with a high ratio
- Modifiying effects of sex on the associations between intakes of Ca and Mg with disease mortality

*Key messages*

- Significant modifying effects of combined Ca/Mg intake ratio, but not Mg or Ca intake alone, on the associations between intakes of Ca and Mg, respectively, with risk of total mortality and coronary heart diseases and possibly cancer
- In contrast to studies conducted in the US, high intake of Mg was related to an increased risk of total mortality among both men and women a similar Mg intake level but a low Ca/Mg intake ratio.
- Sex significantly modified the associations between intakes of Ca and Mg with disease mortality

*Strengths and limitations of this study*

- Population-based prospective design with large sample sizes
- High rates for baseline participation and follow-up

- A unique population with a similar Mg intake, but a lower Ca/Mg intake ratio vs. US population
- Adjustment for many potential confounding factors
- Similar results in sensitivity analysis by excluding those who used Ca or multivitamin supplements
- Caution for the generalization of findings to populations with a high Ca/Mg ratio
- The Ca and Mg contents of drinking water not included
- Small sample size in the analyses by cancer subtype, particularly among men

## INTRODUCTION

Magnesium (Mg) and calcium (Ca) belong to the same family in the periodic table and share the same homeostatic regulating system[1] involving Ca sensing receptor (CaSR) and (re)absorption[2]. Meanwhile, Mg and Ca antagonize each other in many physiologic activities [2-8]. It was not until recently that Mg was thought to share ion transporters with Ca in (re)absorption[9]. Mg ion transporters identified in recent years (e.g. TRPM7) also have affinity for Ca[9]. In the intestine, Ca and Mg may directly or indirectly compete for intestinal absorption [2]. A low concentration of Ca and a high concentration of Mg (thus, a low Ca:Mg) in the lumen activates mucosal transport of Mg [2]. A high Ca intake reduces absorption rates for both Mg and Ca in humans [2;4].

Colon lumen concentrations for $Ca^{2+}$ and $Mg^{2+}$ are monitored by the same receptor, the CaSR [1]. If the body needs to absorb a total of ten ions of Ca and Mg, and the diet contains five ions of Ca and five of Mg, all five Ca and five Mg ions are absorbed. If the diet consists of forty five Ca and five Mg, nine Ca and one Mg are absorbed. Thus, if the total absorbed number of Ca and Mg is relatively constant, the absorption number for Ca is dependent upon Ca*(1/(Ca+Mg)) $=Ca/(Mg+Ca)=(Mg/Ca+1)^{-1}$, in which solely the Mg/Ca ratio varies. It is also true for Mg. Thus, we postulated that the dietary ratio of Ca to Mg modifies the effects of Ca and Mg intakes on carcinogenesis [10;11]. In a study conducted in the US, we found high intake of total Ca or Mg may only be related to a reduced risk of colorectal adenoma when the Ca/Mg ratio was below 2.78 [10]. In a randomized clinical trial conducted in the US, Ca treatment only significantly reduced colorectal adenoma recurrence risk when the baseline dietary Ca/Mg ratio was under 2.63 and this effect modification by the Ca/Mg ratio cannot solely be attributed to the baseline dietary intake in either Ca or Mg[11]. In another study, high serum Ca/Mg ratio was associated with an

increased risk of high-grade prostate cancer after controlling for serum Ca and Mg[12]. However, all these studies have been conducted in high Ca/Mg ratio populations.

Many studies conducted in Western countries have linked low intake of Mg to insulin resistance[13] and systemic inflammation[14] and, thus, risk of diseases common in Western countries, such as metabolic syndrome [15], type II diabetes[16-18], coronary heart disease[19-21] and cancer[10;22-24]. East Asians have much lower incidence and mortality rates of coronary heart disease and colorectal cancer, but much higher rates of stroke compared to their counterparts in US. However, mean intake of Mg [25;26] in East Asia[10] is equivalent to the US population [27] whereas the Ca/Mg intake ratio is almost halved in the Chinese population compared to the US population [25;28]. Thus, it is possible that the differential Ca/Mg intake ratio may contribute, in part, to the different incidence and mortality rates of these common diseases[10].

The US population's low Ca/Mg ratio range defined as below US median) overlaps with the high ratio range in the Chinese population (above Chinese median) (See **Figure 1**). Thus, we further hypothesize that in Chinese populations, intakes of Mg and Ca may only be related to a reduced risk of mortality due to colorectal cancer and, perhaps, other common diseases when dietary Ca/Mg ratio is above median (1.7). Conversely, previous studies indicate that high Mg intake led to a negative Ca balance when Ca intake was low (i.e. low Ca/Mg ratio) [29]. Thus, high Mg intake may have a detrimental effect when Ca/Mg ratio is very low (below 1.7). We tested these hypotheses in two population-based cohorts conducted in China with over 130,000 participants.

## METHODS

***SWHS and SMHS:*** The Shanghai Women's Health Study (SWHS) and the Shanghai Men Health Study (SMHS) are two population-based, prospective cohort studies conducted in urban Shanghai, China. In both studies similar designs which were described in detail elsewhere, were utilized [30;31]. In brief, during 1996 and 2000, the SWHS recruited 74, 942 female participants aged 40 to 70 years from seven urban communities representative of urban Shanghai with a participation rate of 92.7% while from 2002 to 2006, the SMHS enrolled 61, 500 men aged 40 to 74 years from the same seven communities with a participation rate of 74.1%. Certified interviewers elicited information on demographic characteristics, medical history, anthropometrics, usual dietary habits, physical activities, and other lifestyle factors. At least two measurements were conducted for weight, height, and circumferences of the waist and hips at the in-person interview. The study was approved by all relevant institutional review boards in China (Shanghai Cancer Institute) and the United States (Vanderbilt University).

***Cohort follow-up and outcome ascertainment:*** The SWHS and SMHS participants have been followed-up by biennial home visit as well as annual record linkage to the population-based Shanghai Cancer Registry and Vital Statistics Registry. In the current study, the primary outcomes included deaths from all causes, deaths from cardiovascular diseases (including coronary heart diseases and stroke) and deaths from cancers occurring between the baseline recruitment and the most recent follow-up and/or annual vital status linkage. The follow-up rate for vital status in both cohorts was >99.9% complete[32;33]. In this analysis, in order to allow for the delay in records processing, the date of the last follow-up was set as Dec, 31, 2009 for study participants, 6 months before the most recent record linkage (June 30, 2010). The underlying

causes for deaths were determined based primarily on death certificates from Shanghai Vital Statistics Registry which are coded using the *International Classification of Diseases, Ninth Revision* (ICD-9). Studies have been conducted to validate cause-of-death statistics in urban China, which also includes urban Shanghai, and data on death certificates have shown reasonable accuracy for major causes of deaths including cancer and cardiovascular diseases [34].

***Exposure Measurement and Covariates:*** Usual dietary intakes were assessed through in-person interviews using validated food-frequency questionnaires (FFQs) (11,12) in SMHS[35] and SWHS[36]. Nutrient intakes (i.e. dietary Ca and Mg), were derived from FFQs using the Chinese food composition tables (Institute of Nutrition and Food Safety, China CDC, 2004). A wide array of covariates assessed at the baseline survey and FFQs were compared by levels of exposure (intake levels of Ca and Mg) as potential confounding factors (Table 1).

***Statistical Analysis*** To be consistent with SMHS, we excluded from the analysis 1,579 subjects with a history of cancer at baseline from the SWHS. We also excluded 126 subjects in SWHS and 70 in SMHS with unreasonably high or low energy intake (<500 or >3,500 kcal/day for women; <500 or >4,200 kcal/day for men), and 8 subjects in SWHS and 14 in SMHS who moved away from Shanghai immediately after the baseline survey. As a result, a total of 73,232 for SWHS and 61,414 for SMHS were included in the final analyses.

We estimated the main associations using hazard ratio (HR) in Cox proportional hazard regression models[37], using age at entry and age at death or age at censor as a time-scale[38]. To be consistent with previous cohort studies which evaluated the association of Ca and Mg with

disease risks[10;22;23], we have adjusted for the following potential confounding factors: age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng (yes, no), alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium and zinc. Log-transformation was conducted for continuous variables. We have adjusted for age to control for potential birth cohort effect. We have additionally adjusted for postmenopausal hormone use, but the associations did not change.

Determination of low, medium and high exposure categories: since intake level of Mg in our study population is comparable to the studies conducted in Western countries, we have used the US's Mg Recommended Daily Allowance (RDA) for women (320 mg/day), which is very close to the 66th percentile of Mg intake in our study population (321 mg/day), as the upper cutpoint. In contrast, very few study participants had a Ca intake level above the current US Daily Reference Intake (DRI) for Ca (1000 mg/day). Thus, we have used 600 mg/day, a previous Ca DRI for Chinese (Institute of Nutrition and Food Safety and Chinese Institute for Preventive Medicine, 1991), as the upper cutpoint. We utilized the medians of Mg and Ca for the remaining participants as the lower cutpoint. Since the intake levels of Mg and Ca in men were higher than women, we have added one cutpoint (i.e. US RDA for Mg in men (420 mg/day)) for Mg and one cutpoint (i.e. the current DRI for Ca in Chinese adults (800 mg/day)) for Ca in the analysis for men.

Separate analyses were conducted for SWHS (women) and SMHS (men). The first model was adjusted for age and other confounding factors except for Ca and Mg. In the second model, Ca

and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively. Stratified analyses by medians of Ca/Mg ratio[10;11], Ca or Mg intake[11] were conducted. In the stratified analyses, the full-adjusted (second) model was used. In addition, we have conducted sensitivity analyses by excluding those who took Ca supplement or multivitamin. Multiplicative interactions between continuous Mg or Ca and continuous Ca/Mg ratio were tested. Tests for trend across exposure categories were performed by entering the categorical variables as a continuous variable in the model. *P* values of < 0.05 (2-sided probability) were interpreted as being statistically significant. Statistical analyses were conducted by using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

**RESULTS**

Selected demographic characteristics and potentially confounding factors were compared by intake levels of Ca and Mg separately for SWHS and SMHS as shown in **Table 1**. Proportions of participants with high educational achievement, female alcohol drinkers, tea drinkers, users of Ca, multivitamin and ginseng supplements, and those who were physically active and consumed high levels of (energy- and age-adjusted) saturated fatty acids, fiber, phosphorus, retinol, vitamin E, folate, sodium, potassium, zinc and Mg or Ca increased with increasing intakes of Ca and Mg. The proportion of participants that smoked, male alcohol drinkers, and those who were not married decreased with increasing intakes of Ca and Mg.

In the pooled analysis of SMHS and SWHS (Data not shown), we found that sex significantly modified the associations between intakes of Ca and Mg with risk of total mortality (*P* for

interactions < 0.01) and mortality due to cardiovascular diseases (*P* for interactions < 0.01). Sex also appeared to modify the associations of Ca and Mg with cancer (*P* for interactions were 0.125 for Mg and 0.280 for Ca, respectively). Thus, separate analyses were conducted for SWHS and SMHS.

Presented in **Table 2** are the associations of dietary intakes of Ca and Mg with risk of total mortality, mortality due to cardiovascular diseases and cancer in SWHS. After adjusting for potentially confounding factors (model 1) and additionally controlling for Ca or Mg, respectively (model 2), we found that among women, high intake of Mg was significantly associated with 35-50% increased risks of mortality due to cardiovascular diseases, particularly stroke. Furthermore, Ca/Mg ratio modified the associations between intake of Mg and risk of total mortality (*P* for interaction, 0.07) and mortality due to coronary heart diseases (*P* for interaction, 0.02) in model 2. Among those with Ca/Mg ratio ≤ 1.7, intake of Mg was significantly associated with 24% -66% increased risks of total mortality and mortality due to cardiovascular diseases (including stroke and coronary heart disease), and an 120% increased risk of colorectal cancer (P for trend, 0.05). On the other hand, among those with Ca/Mg intake ratio > 1.7, intake of Mg was related to a decreased risk of lung cancer (P for trend, 0.01); and intake of Ca was associated with significantly reduced risk of cancer (P for trend, 0.02) including lung cancer (P for trend, 0.01) and colorectal cancer (P for trend, 0.05), but was related to an increased risk of gastric cancer. We did not present the results for other GI tract cancers because the sample sizes for mortality due to these gastrointestinal tract cancers are sparse and not reliable. The findings were also not statistically significant. In the sensitivity analyses conducted by excluding those who used Ca or multivitamin supplements, similar results were observed (Data not shown).

We found the association patterns with Ca and Mg differed in women (SWHS) and men (SMHS). Because the differential associations could potentially be caused by use of different sex-specific cutpoints we chose to evaluate first the associations using common cutpoints (Tables 2 and 3). Thus, **Table 3** shows the associations between dietary intakes of Ca and Mg and risk of total mortality, mortality due to cardiovascular diseases and cancer in SMHS using the same cutpoints as those for women in SWHS (Table 2). Among men, high intake of Ca (≥600 mg/day) were related to reduced risks of total mortality and mortality due to cardiovascular diseases and, possibly, cancer while intake of Mg (≥320 mg/day) was possibly related to a reduced risk of death due to coronary heart diseases. In the stratified analysis (model 2), we found the associations between intakes of Ca and Mg and risk of total mortality and cardiovascular diseases were modified by Ca/Mg ratio with the *p* for interactions ranging from 0.01 to 0.07. Among participants with Ca/Mg intake ratio > 1.7, risks of total mortality, and mortality due to coronary heart disease and cancer were significantly reduced with increasing intakes of Ca and Mg. These associations were statistically significant except for the non-significant inverse association between Mg and cancer. In contrast, among those with Ca/Mg ratio ≤ 1.7, intakes of Ca and Mg were not significantly related to risks. The sample size became very sparse in the analysis for subtype cancers due to a shorter follow-up time for SMHS (men) compared to SWHS (women) and none of the associations was significant (Data not shown). Analyses limited to those who did not use Ca or multivitamin supplements generated similar results (Data not shown).

Men had higher intake levels of Ca and Mg than women. In **Table 4**, we repeated the analyses presented in Table 3, but added one cutpoint (420 mg/day, RDA for US men) for Mg and one cutpoint (800 mg/day, the current DRI for Chinese) for Ca. We found that highest intake of Mg (≥420 mg/day) was significantly associated with increased risks of total mortality and mortality due to cancer. We also found Ca intake levels between 600-800 mg/day, but not higher than 800 mg/day, may be associated with reduced risks of total mortality and mortality due to cardiovascular diseases and cancer. It is worth noting at borderline significance, high Ca intake was associated with a reduced risk of death due to colorectal cancer while Mg intake was associated with an increased risk of gastric cancer mortality, particularly among those with Ca/Mg ratio ≤1.7 (*P* for interaction, 0.05). Analyses limited to those who did not use Ca or multivitamin supplements generated similar results (Data not shown).

We have also conducted stratified analyses to examine whether Ca intake directly interacted with Mg intake in relation to risk of total mortality, mortality due to cardiovascular diseases (coronary heart diseases and stroke) and cancer. For both men and women, we found Mg intake was associated with a significantly increased risk of total mortality among those with Ca intake equal to or below median, but was associated with a significantly reduced risk among those with Ca intake above the median (**Table 5**). Among men Ca intake was associated with a reduced risk of total mortality when Mg intake was above the median while Ca intake was not significantly associated with the risk among those with Mg intake below the median. Similar findings were observed for women although none of the association was statistically significant. These findings indicate a pattern for interactions between Ca and Mg. However, Ca-Mg interactions were not statistically significant for total mortality (Table 5), and mortality due to cardiovascular diseases

(coronary heart diseases and stoke) and cancer and its subtypes in both SWHS and SMHS (Data not shown).

## DISCUSSION

### Statement of principal findings

In contrast to studies conducted in the US with a high Ca/Mg ratio which generally found inverse associations, we found in Chinese populations with a low Ca/Mg intake ratio that high intake of Mg (≥320 mg/day for women and ≥420 mg/day for men) was overall related to an increased risk of total mortality among both men and women, mortality due to cardiovascular diseases among women and mortality due to cancer among men after mutually adjusting for intake of Ca and other confounding factors. Furthermore, we found that Ca/Mg ratio significantly modified the associations between intakes of Ca and Mg with risk of total mortality and coronary heart diseases and possibly cancer whereas we did not identify any significant interactions between Ca and Mg in relation to these outcomes. Among those with Ca/Mg ratios above the median, intakes of Ca and Mg were associated with reduced risks of total mortality, and mortality due to coronary heart diseases for both men and women, and cancer for men while Mg intake was associated with a decreased risk of cancer mortality for women. Conversely, among those with Ca/Mg ratio equal to or below the median, intake of Mg was associated with increased risks of total mortality and mortality due to cardiovascular diseases for men and women as well as colorectal cancer for women and possibly gastric cancer for men.

### Hypothesis and overall biological mechanism

Ionized Ca has a central role in cellular signaling [39], controlling numerous cellular processes [40], while ionized Mg is essential in over 300 biological activities[8]. Ca and Mg have similar chemical properties and share the same homeostatic regulating system including gut absorption and kidney reabsorption to maintain a normal balance of Ca and Mg[1]. Furthermore, the changes in blood or colon lumen concentrations for $Ca^{2+}$ and $Mg^{2+}$ are monitored by the same receptor, the calcium-sensing receptor (CaSR) [1]. Once the Ca or Mg concentration is high, CaSR could respond to it even if the concentration of Mg or Ca, respectively, is low, resulting in the simultaneous depression of the (re)absorption process for both Ca and Mg[2;4]. Thus, in clinics, hypomagnesemia is commonly linked to secondary hypocalciuria[41]. Previous studies also showed that changes in the dietary Ca/Mg balance affected systemic inflammation responses in animal models [3;14]. In addition to inflammation, $Mg^{2+}$ and $Ca^{2+}$ potentially antagonize each other in many other physiologic activities, such as oxidative stress[42] and insulin resistance [18;43], DNA repair, cell differentiation and proliferation, apoptosis, and angiogenesis [3;6;44], which may also be involved in development of cancer, cardiovascular diseases and many other diseases. As we mentioned in the introduction, if the total absorbed number of Ca and Mg ions is relatively constant, the absorbed numbers of Ca and Mg are dependent on Ca/Mg ratio in the gut. Therefore, the Ca/Mg ratio to which gut epithelial cells are directly exposed may modify absorption of Ca and Mg and other activities in gut[10;11].

**Comparison with previous studies**

*Possible explanations on findings with colorectal cancer:* In 2007, we reported from a study conducted in US that Mg intake from dietary source was only related to a non-significantly reduced risk of colorectal adenoma while total Mg intake from both dietary and supplemental

source was associated with a significantly reduced risk [10]. The inverse associations with both total intakes of Ca or Mg may primarily appear among those with Ca/Mg ratio was below 2.78 [10]. Similar to our finding, in a very recent case-control study conducted in Netherlands, Wark et al. found dietary Mg only (not including Mg from supplementation) was marginally significantly related to a reduced risk of colorectal adenoma[45]. In our 2007 report, we found the p for interaction between total Mg and total Ca/Mg ratio was 0.10[10] whereas p for interaction was 0.65 between dietary Mg and dietary Ca/Mg ratio. Interestingly, the study conducted by Wark et al. also did not find a significant interaction between dietary Mg and dietary Ca/Mg ratio (p for interaction=0.86)[45]. It is possible that misclassification in the analyses due to only using Ca and Mg from dietary source may bias the result to the null. In a recent paper based on the analysis of a large clinical trial, Ca supplementation reduced risk of colorectal adenoma recurrence only among those with baseline dietary Ca/Mg ratio less than or equal to 2.63[10;11]. Moreover, the effect of Ca treatment did not significantly differ by baseline intake of Ca or Mg alone[11;46]. Zhang et al found in the Nurses' Health Study, the interaction between total Ca and Mg intakes (p for interaction, 0.17) was also not statistically significant in relation to risk of colorectal cancer incidence[47].

*Overall interpretations for findings on diseases other than colorectal cancer:* Consistent with these published findings on colorectal neoplasia, we found in the current study that the associations between Ca or Mg with total mortality and mortality due to cardiovascular diseases and cancer were not significantly modified by Mg or Ca, respectively, but many of these associations were significantly modified by Ca/Mg ratio. In a recent study, we found high serum Ca/Mg ratio was statistically associated with an increased risk of high-grade prostate

cancer even after adjusting for both serum Ca and Mg[12], indicating that the balance between Ca and Mg may affect risk or pathogenesis of diseases other than colorectal cancer or adenoma. In addition to competition for absorption, a previous study found that Mg supplementation increased urinary Ca excretion if intake of Ca was <800 mg/day[29], suggesting that Mg may suppress Ca reabsorption when Ca/Mg intake ratio is very low. It is possible that the Ca and Mg statuses in the body and specific organs or tissues could be indirectly modified by the dietary Ca/Mg ratio through affecting both absorption and reabsorption processes [29;48]. As a result, it is not surprising that we found the dietary Ca/Mg ratio also modified the effects of Ca and Mg on risk of diseases occurring in organs which do not directly expose to dietary Ca and Mg. However, it is conceivable through the homeostasis regulation by (re)absorption, the Ca/Mg ratio in the gut differs from that in circulation and other systems. Thus, the modification effects of dietary Ca/Mg ratio may become weaker on diseases occurring in organs other than the digestive tract. For example, among women with Ca/Mg ratio ≤ 1.7, high intake of Mg was associated with a 24% of increased risk of total mortality and 66% increased of coronary heart disease death compared to 120% increased risk for colorectal cancer death. Among women with Ca/Mg >1.7, intake of Ca has the strongest inverse association with gastrointestinal cancer.

*Comparison with studies on association of Mg with CVD:* The associations between Mg intake with risk of stroke [49;50] and coronary heart disease [49;51]incidence and death have not been entirely consistent in previous prospective studies. Two meta-analyses found that Mg intake was related to a significantly reduced risk of stroke [49;50]. However, the inverse association was weak and only existed with ischemic stroke, but not hemorrhagic stroke [50]. Also, a previous meta-analysis found Mg intake was non-significantly inversely associated with coronary heart disease[49]. No

study has examined the possible effect modifications by the Ca/Mg ratio. A very recent report from the JACC study conducted in Japan, a population also with a low Ca/Mg ratio, found that dietary intake of Mg was significantly related to reduced risks of mortality due to hemorrhagic stroke in men and cardiovascular diseases in women [51]. However, after adjusting for intakes of Ca and potassium, all these inverse associations not only disappeared, but further became positive associations, which were significant for total stroke in women with an HR (95% CI) of 1.81(1.12-2.94) for the highest quintile intake vs. the lowest (*P* for trend, 0.015) and of borderline significance for ischemic stroke in women (*P* for trend, 0.081). Thus, these findings from the study conducted in a Japanese population are consistent with what we found in Chinese populations. Furthermore, previous cohort studies have relatively consistently found high dietary intake of Mg was associated with a reduced risk of metabolic syndrome [15] and type II diabetes [16-18] and insulin resistance [13] in Western populations. However, clinical trials using different high doses of Mg supplementations led to inconsistent results on glycaemic control among diabetes patients[52]. The null effect in many of these trials could be due to a high dose of Mg supplementation resulting in a very low Ca/Mg ratio (<1.7). Future studies are needed to confirm this possibility.

*Comparison with studies on association of Ca with CVD:* Similar to Mg, previous cohort studies have also provided inconsistent results on the associations between Ca intake and supplemental use of Ca and risk of cardiovascular diseases[53;54]. Meta-analysis of these studies showed a non-significant result with either coronary heart disease or stroke [53]. No study has examined whether the Ca/Mg ratio modifies the association between Ca intake and risk of cardiovascular disease incidence or death. A recent study conducted among a population with a high intake level of

Mg found intake of Ca, but not Mg, to be associated with a reduced risk of total mortality and, likely, mortality due to cardiovascular diseases [54]. In joint analysis, intake of Ca was significantly related to a reduced risk of total mortality only when intake of Mg was under 480 mg/day. It is very important to mention that this study was conducted in a population located in the northern latitude where sunlight is very limited for vitamin D synthesis from autumn to spring [55]. Furthermore, the investigators excluded those who took dietary supplements including vitamin D supplements from the study. As a result, the average intake level of vitamin D was as low as 6.5 µg / day. Thus, it is expected in a population at high risk of vitamin D deficiency that Ca intake would be related to a reduced risk of total mortality even at a very high level, particularly among those with relatively low intake of Mg (no absorption competition from Mg). In contrast, although still controversial, recent findings from reanalysis of the Women's Health Initiative study and meta-analysis of secondary clinical trials data conducted among populations with high Ca/Mg ratio suggest that high Ca supplementation with or without vitamin D may modestly increase the risk of cardiovascular events, especially myocardial infarction[56;57]. Also, we found Ca intake levels between 600-800 mg/day, but not higher than 800 mg/day, may be associated with reduced risks of total mortality and mortality due to cardiovascular diseases and cancer. Our finding is supported by the results from both the Nurses' Health Study and the Health Professionals Follow-up Study. In these two studies, the furthest reduction in risk of colorectal cancer associated with intake of Ca was achieved by intakes of 700-800 mg/day, but no additional reduction in risk was observed at higher intakes of Ca [58].

In additional analysis in the JACC, the reduction in risk of mortality due to coronary heart disease was only significant among those with both high intakes of Ca and Mg compared to

those with both low intakes[51]. This finding indicates that high Ca plus high Mg, not high Ca or Mg alone was significantly associated with a reduced risk. The Ca/Mg ratio for people who had both high Ca and high Mg intakes or those with both low Ca and low Mg intakes is in the middle range (i.e. smaller than those with a high Ca and a low Mg intake, but greater than those with a low Ca and a high Mg intake). Among those with a Ca/Mg ratio in the middle, high intakes of Ca and Mg had a reduced risk compared to those with low intakes of Ca and Mg. Thus, this joint association between Ca with Mg found in the JACC is in general consistent with the modifying effects by Ca/Mg ratio observed in the current study. We have also replicated this joint analysis in the current study and found a similar finding among men, but not women. Also, in the current study, we found many significant interactions between Ca/Mg ratio with Ca or Mg, but zero significant interactions between Ca and Mg intakes in relation to disease mortality, suggesting Ca/Mg ratio has a stronger modifying effect than Ca or Mg alone. The fact is also consistent with that predicted mathematically.

*Possible interpretations on the sex modification:* In the current study of a population with a low dietary Ca/Mg ratio, we found Mg intake (≥320 mg/day) among women and a higher dose among men (i.e. Mg intake ≥420 mg/day) was related to an increased risk of total mortality. Furthermore, we found the associations between intakes of Ca and Mg and risk of total mortality and mortality due to cardiovascular diseases significantly differed by sex. These findings are biologically meaningful because of the effects of estrogen on Mg and Ca metabolism [59]. For example, estrogen shifted Mg from circulation (serum) into cells and, thus, lower Mg intake was required for young women than young men to keep positive magnesium balance[59]. Seelig proposed that the increase of the Ca/Mg intake ratio from 2.0 in 1920s to over 3.0 in the US

contributed to a sharp rise in incidence of cardiovascular diseases in men, but not women[59] and this ratio is continuously rising in recent years[60]. Some previous cohort studies conducted in populations with high Ca/Mg ratio have also provided some support. For example, the Atherosclerosis Risk in Communities study found an inverse association between Mg intake and serum Mg and risk of coronary heart disease in men, but not in women and *P* for interaction was 0.07 for serum Mg with sex [61]. Although a meta-analysis association for cohort studies was not significant, all studies conducted among men had an RR/HR under 1.00 for the association between Mg intake and risk of coronary heart disease while only two studies conducted among women had an RR/HR above 1.00[49]. Mg was weakly, but significantly associated with a reduced risk of stroke in a very recent meta-analysis[50]. However, Health Professionals' Follow-up Study found an inverse association between Mg intake and risk of stroke, particularly among men with hypertension, whereas Mg intake was not related to risk among Nurses' Health Study[49]. Further studies are necessary to understand the potential sex modifications.

*Interesting preliminary observations on gastric cancer and stroke:* One interesting, but preliminary, observation in the current study is that Mg intake may be associated with an increased risk of deaths due to stroke and gastric cancer (among men). Previous studies found that compared to the world average, the Chinese population had a much lower incidence and mortality rate of coronary diseases, but a much higher incidence and mortality rate of stroke; [62] and China is also among the regions with the highest rate of gastric cancer, particularly among men[63]. It is possible that the low Ca/Mg ratio in Chinese populations may partially contribute to the higher risks. However, further studies are necessary to explore this possibility.

**Strengths and weaknesses**

The strengths include a population-based prospective design, large sample size, and high rates for baseline participation and follow-up, which minimize potential differential recall bias or selection bias. The current study has been conducted in a population with a low Ca/Mg intake ratio. Thus, caution should be used to generalize our findings to populations with a high Ca/Mg ratio before further studies have been conducted to examine whether Ca/Mg ratio or Mg and Ca modifies the associations of Ca and Mg intakes with risk of non-gastrointestinal diseases [10;11] in populations with a high Ca/Mg ratio. We have adjusted for many potential confounding factors, including Ca supplement and multivitamin use, and also found similar results in sensitivity analysis by excluding those who used Ca or multivitamin supplements. However, the Ca and Mg contents of drinking water could not be calculated. This may lead to non-differential misclassification of Ca and Mg intake, which usually biases associations toward the null. Finally, sample size became smaller in the analyses by cancer subtype, particularly among men. Thus, some of the null associations in subtype analysis could be due to a small sample.

**Conclusion and clinical and public health implications**

In the current study conducted in populations with lower Ca/Mg ratios, we found that when the Ca/Mg ratio was above 1.7, high intake of Ca was related to a reduced risk of colorectal cancer death and the reduction in risk was the strongest among all the associations between Ca and disease mortality. Conversely, among those with Ca/Mg ratio less than or equal to 1.7, high intake of Mg was related to a significantly increased risk of mortality due to colorectal cancer in women. Collectively, the findings from the current study as well as some previous studies conducted in populations with high Ca/Mg ratios [10;11] indicate that a Ca/Mg ratio between 1.70

and 2.63 may be required for high intakes of Ca and Mg to be protective against colorectal cancer.

In addition to colorectal cancer, the potential modifications by the dietary Ca/Mg ratio and sex may provide possible explanations for the inconsistencies on the associations between intake of Ca and Mg with risk of coronary heart diseases[49;53;54], stroke[49;50;53] and total cancer [54;64] in previous studies.

Future studies are necessary to confirm our finding of modifying effects of the Ca/Mg ratio and to define the optimal Ca/Mg intake ratio range. Our findings, if confirmed, will have a very important public health significance, including selecting optimal doses in the intervention trials and in the prevention strategy development for many common diseases. Furthermore, Ca/Mg ratio should be taken into account when the new RDA or DRI levels of Ca and Mg are developed. For example, lower RDA or DRI levels of Mg for men and women may be required for Chinese populations because they have a low Ca/Mg intake ratio.

**Contributors:** DQ developed the hypothesis and drafted manuscript, and had primary responsibility for final content; WZ, XOS, and WHC designed, directed and obtained funding for the parent studies, and contributed to revisions, and data interpretation of the paper; XD and HC contributed to the data analysis, manuscript revisions, and data interpretation; GY, YTG, YBX, and HL contributed to the study design, data collection of the parent studies, manuscript revisions, and data interpretation; MJS and BJ contributed to the manuscript revisions, and data interpretation of the paper.

**Source of funding:** This study was supported by USPHS grant R37CA70867 and R01CA082729 from the National Institutes of Health. Part of Dr. Dai's effort on the study has been supported by R37CA70867, R01CA082729, R01 AT004660 and R01 CA149633 from National Cancer Institute, Department of Health and Human Services and AICR #08A074-REV from the American Institute for Cancer Research.

The funding sponsor had no role in study design, data collection, statistical analysis and result interpretation, the writing of the report, and the decision to submit for publication. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

**Study approval:** Institutional review board

**Competing interests:** None

**Data sharing**: No additional data available.

## ACKNOWLEDGMENTS

The authors would like to thank the participants and staff for the SWHS and SMHS. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## REFERENCE

(1) Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* 2001; 81(1):239-297.

(2) Hardwick LL, Jones MR, Brautbar N, Lee DB. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. *J Nutr* 1991; 121(1):13-23.

(3) Bussiere FI, Gueux E, Rock E, Mazur A, Rayssiguier Y. Protective effect of calcium deficiency on the inflammatory response in magnesium-deficient rats. *Eur J Nutr* 2002; 41(5):197-202.

(4) Norman DA, Fordtran JS, Brinkley LJ, Zerwekh JE, Nicar MJ, Strowig SM et al. Jejunal and ileal adaptation to alterations in dietary calcium: changes in calcium and magnesium absorption and pathogenetic role of parathyroid hormone and 1,25-dihydroxyvitamin D. *J Clin Invest* 1981; 67(6):1599-1603.

(5) Nielsen FH, Milne DB, Gallagher S, Johnson L, Hoverson B. Moderate magnesium deprivation results in calcium retention and altered potassium and phosphorus excretion by postmenopausal women. *Magnes Res* 2007; 20(1):19-31.

(6) Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J* 1984; 108(1):188-193.

(7) SEELIG MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. *Magnes Res* 1990; 3(3):197-215.

(8) Flatman PW. Mechanisms of magnesium transport. *Annu Rev Physiol* 1991; 53:259-271.

(9) Hoenderop JG, Bindels RJ. Epithelial Ca2+ and Mg2+ channels in health and disease. *J Am Soc Nephrol* 2005; 16(1):15-26.

(10) Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE et al. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007; 86(3):743-751.

(11) Dai Q, Sandler RS, Barry EL, Summers RW, Grau MV, Baron JA. Calcium, Magnesium, and Colorectal Adenoma Recurrence: Results from a Randomized Trial . Epidemiology. In press 2012.

(12) Dai Q, Motley SS, Smith JA, Jr., Concepcion R, Barocas D, Byerly S et al. Blood magnesium, and the interaction with calcium, on the risk of high-grade prostate cancer. *PLoS One* 2011; 6(4):e18237.

(13) Manolio TA, Savage PJ, Burke GL, Hilner JE, Liu K, Orchard TJ et al. Correlates of fasting insulin levels in young adults: the CARDIA study. *J Clin Epidemiol* 1991; 44(6):571-578.

(14) Ziegler D. Type 2 diabetes as an inflammatory cardiovascular disorder. *Curr Mol Med* 2005; 5(3):309-322.

(15) He K, Liu K, Daviglus ML, Morris SJ, Loria CM, van HL et al. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; 113(13):1675-1682.

(16) Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 1992; 55(5):1018-1023.

(17) Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004; 27(1):134-140.

(18) Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27(1):59-65.

(19) Singh RB. Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnes Trace Elem* 1990; 9(3):143-151.

(20) Al Delaimy WK, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Magnesium intake and risk of coronary heart disease among men. *J Am Coll Nutr* 2004; 23(1):63-70.

(21) Dong JY, Xun P, He K, Qin LQ. Magnesium Intake and Risk of Type 2 Diabetes: Meta-analysis of prospective cohort studies. *Diabetes Care* 2011; 34(9):2116-2122.

(22) Larsson SC, Bergkvist L, Wolk A. Magnesium intake in relation to risk of colorectal cancer in women. *JAMA* 2005; 293(1):86-89.

(23) Folsom AR, Hong CP. Magnesium intake and reduced risk of colon cancer in a prospective study of women. *Am J Epidemiol* 2006; 163(3):232-235.

(24) van den Brandt PA, Smits KM, Goldbohm RA, Weijenberg MP. Magnesium intake and colorectal cancer risk in the Netherlands Cohort Study. *Br J Cancer* 2007; 96(3):510-513.

(25) Cai H, Shu XO, Hebert JR, Jin F, Yang G, Liu DK et al. Variation in nutrient intakes among women in Shanghai, China. *Eur J Clin Nutr* 2004; 58(12):1604-1611.

(26) Cai H, Yang G, Xiang YB, Hebert JR, Liu DK, Zheng W et al. Sources of variation in nutrient intakes among men in Shanghai, China. *Public Health Nutr* 2005; 8(8):1293-1299.

(27) Ervin RB, Wang CY, Wright JD, Kennedy-Stephenson J. Dietary intake of selected minerals for the United States population: 1999-2000. *Adv Data* 2004;(341):1-5.

(28) SEELIG MS. THE REQUIREMENT OF MAGNESIUM BY THE NORMAL ADULT. SUMMARY AND ANALYSIS OF PUBLISHED DATA. *Am J Clin Nutr* 1964; 14:242-290.

(29) Spencer H, Fuller H, Norris C, Williams D. Effect of magnesium on the intestinal absorption of calcium in man. *J Am Coll Nutr* 1994; 13(5):485-492.

(30) Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol* 2005; 162(11):1123-1131.

(31) Cai H, Shu XO, Gao YT, Li H, Yang G, Zheng W. A prospective study of dietary patterns and mortality in Chinese women. *Epidemiology* 2007; 18(3):393-401.

(32) Dai Q, Shu XO, Li H, Yang G, Shrubsole MJ, Cai H et al. Is green tea drinking associated with a later onset of breast cancer? *Ann Epidemiol* 2010; 20(1):74-81.

(33) Zhang X, Shu XO, Xiang YB, Yang G, Li H, Gao J et al. Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. *Am J Clin Nutr* 2011; 94(1):240-246.

(34) Rao C, Yang G, Hu J, Ma J, Xia W, Lopez AD. Validation of cause-of-death statistics in urban China. *Int J Epidemiol* 2007; 36(3):642-651.

(35) Villegas R, Yang G, Liu D, Xiang YB, Cai H, Zheng W et al. Validity and reproducibility of the food-frequency questionnaire used in the Shanghai men's health study. *Br J Nutr* 2007; 97(5):993-1000.

(36) Shu XO, Yang G, Jin F, Liu D, Kushi L, Wen W et al. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. *Eur J Clin Nutr* 2003; 58(1):17-23.

(37) Hosmer DW, Lemeshow S. Applied survival analysis. Regression modeling of time to even data. New York: Wiley; 1999.

(38) Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997; 145(1):72-80.

(39) Berridge MJ, Bootman MD, Lipp P. Calcium--a life and death signal. *Nature* 1998; 395(6703):645-648.

(40) Bootman MD, Berridge MJ. The elemental principles of calcium signaling. *Cell* 1995; 83(5):675-678.

(41) Schlingmann KP, Konrad M, Seyberth HW. Genetics of hereditary disorders of magnesium homeostasis. *Pediatr Nephrol* 2004; 19(1):13-25.

(42) Hans CP, Chaudhary DP, Bansal DD. Effect of magnesium supplementation on oxidative stress in alloxanic diabetic rats. *Magnes Res* 2003; 16(1):13-19.

(43) Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesauro P, Varricchio M et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992; 55(6):1161-1167.

(44) Wolf FI, Maier JA, Nasulewicz A, Feillet-Coudray C, Simonacci M, Mazur A et al. Magnesium and neoplasia: From carcinogenesis to tumor growth and progression or treatment. *Arch Biochem Biophys* 2006.

(45) Wark PA, Lau R, Norat T, Kampman E. Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis. *Am J Clin Nutr* 2012.

(46) Wallace K, Baron JA, Cole BF, Sandler RS, Karagas MR, Beach MA et al. Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; 96(12):921-925.

(47) Zhang X, Giovannucci EL, Wu K, Smith-Warner SA, Fuchs CS, Pollak M et al. Magnesium intake, plasma C-peptide, and colorectal cancer incidence in US women: a 28-year follow-up study. *Br J Cancer* 2012; 106(7):1335-1341.

(48) Sahota O, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int* 2006; 17(7):1013-1021.

(49) Song Y, Manson JE, Cook NR, Albert CM, Buring JE, Liu S. Dietary magnesium intake and risk of cardiovascular disease among women. *Am J Cardiol* 2005; 96(8):1135-1141.

(50) Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *Am J Clin Nutr* 2012; 95(2):362-366.

(51) Zhang W, Iso H, Ohira T, Date C, Tamakoshi A. Associations of dietary magnesium intake with mortality from cardiovascular disease: The JACC study. *Atherosclerosis* 2012.

(52) Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med* 2006; 23(10):1050-1056.

(53) Wang L, Manson JE, Sesso HD. Calcium Intake and Risk of Cardiovascular Disease: A Review of Prospective Studies and Randomized Clinical Trials. *Am J Cardiovasc Drugs* 2012.

(54) Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, Wolk A. Dietary calcium and magnesium intake and mortality: a prospective study of men. *Am J Epidemiol* 2010; 171(7):801-807.

(55) Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. *JAMA* 2005; 294(18):2336-2341.

(56) Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011; 342:d2040.

(57) Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; 341:c3691.

(58) Giovannucci E. Diet, body weight, and colorectal cancer: a summary of the epidemiologic evidence. *J Womens Health (Larchmt )* 2003; 12(2):173-182.

(59) SEELIG MS, Altura BM, Altura BT. Benefits and risks of sex hormone replacement in postmenopausal women. *J Am Coll Nutr* 2004; 23(5):482S-496S.

(60) Rosanoff A. Rising Ca:Mg intake ratio from food in USA Adults: a concern? *Magnes Res* 2010; 23(4):S181-S193.

(61) Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 1998; 136(3):480-490.

(62) Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. *Circulation* 2001; 103(3):462-468.

(63) Parkin DM, Whelen SL, Ferlay J, Raymond L. Cancer Incidence in Five Continents. [7]. 1997. Lyon, International Agency for Research on Cancer.

(64) Li K, Kaaks R, Linseisen J, Rohrmann S. Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg). *Cancer Causes Control* 2011.

**Table 1. Baseline Lifestyle Factors and Demographics by Intakes of calcium and magnesium, the Shanghai Women's Health Study(SWHS) and the Shanghai Men Health Study (SMHS), 1996-2009**

| | Calcium (mg/day) | | | Magnesium (mg/day) | | |
|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | <251 | 251-<320 | ≥320 |
| **Shanghai Women's Health Study** | | | | | | |
| **Married, %** | 87.87 | 90.28 | 88.45 | 87.93 | 89.87 | 88.96 |
| **Smokers, %** | 3.64 | 2.13 | 2.07 | 3.41 | 2.18 | 2.5 |
| **Alcohol drinkers, %** | 2.08 | 2.17 | 2.7 | 2.11 | 2.08 | 2.7 |
| **Tea drinker, %** | 24.84 | 32.23 | 36.22 | 26.09 | 31.4 | 34.24 |
| **Ginseng use, %** | 25.01 | 30.35 | 34.85 | 26.75 | 29.94 | 31.55 |
| **Ca Supplement use, %** | 15.41 | 20.33 | 25.09 | 17.49 | 19.75 | 21.43 |
| **Multivitamin use, %** | 3.98 | 8.1 | 11.68 | 5.74 | 7.52 | 8.77 |
| **Physically active, %** | 30.12 | 36.06 | 43.32 | 31.78 | 35.64 | 39.79 |
| **High school or up , %** | 8.75 | 15.55 | 19.78 | 10.82 | 15.2 | 15.77 |
| **Age (years), mean (SD)** | 53.37(9.45) | 51.88(8.79) | 51.85(8.54) | 53.48(9.55) | 51.95(8.74) | 51.68(8.45) |
| **BMI(kg/m2), mean (SD)** | 24.18(3.53) | 23.83(3.36) | 23.96(3.28) | 23.85(3.46) | 24.00(3.38) | 24.29(3.40) |
| **Daily nutrient intake adjusted for age and total energy, except for total energy** | | | | | | |
| **Total energy** [a] | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) | 1673.77(0.00) |
| **Saturated fat** | 7.02(0.02) | 8.99(0.02) | 10.99(0.03) | 7.89(0.02) | 8.62(0.02) | 9.65(0.03) |
| **Fiber** | 9.55(0.02) | 11.15(0.02) | 13.51(0.03) | 8.26(0.02) | 11.17(0.02) | 15.26(0.03) |
| **Phosphorus** | 852.77(0.63) | 985.46(0.66) | 1162.48(0.91) | 843.66(0.85) | 975.56(0.77) | 1161.18(1.16) |
| **Calcium** | 310.97(0.54) | 493.36(0.57) | 726.90(0.78) | 335.37(0.99) | 476.36(0.90) | 668.24(1.34) |
| **Magnesium** | 246.51(0.21) | 279.27(0.22) | 329.68(0.30) | 231.88(0.23) | 278.50(0.21) | 347.30(0.31) |
| **Retinol** | 146.88(0.95) | 186.49(1.00) | 228.98(1.37) | 163.43(1.14) | 178.50(1.03) | 203.98(1.55) |
| **Vitamin E** | 10.72(0.02) | 13.68(0.03) | 18.63(0.03) | 9.87(0.03) | 13.61(0.03) | 19.39(0.04) |
| **Folate** | 254.15(0.43) | 295.56(0.45) | 356.16(0.62) | 227.05(0.47) | 296.25(0.43) | 391.14(0.64) |
| **Sodium** | 252.92(0.52) | 355.20(0.55) | 489.11(0.75) | 260.13(0.73) | 345.16(0.67) | 467.53(1.00) |
| **Potassium** | 1479.84(2.17) | 1826.56(2.28) | 2293.21(3.14) | 1360.48(2.48) | 1808.59(2.25) | 2440.75(3.38) |
| **Zinc** | 10.20(0.01) | 10.85(0.01) | 11.84(0.01) | 10.02(0.01) | 10.83(0.01) | 12.02(0.01) |
| **Shanghai Men's Health Study** | | | | | | |
| **Married, %** | 96.37 | 97.37 | 97.70 | 96.48 | 97.44 | 97.57 |
| **Smokers, %** | 76.18 | 70.32 | 65.45 | 72.67 | 69.22 | 68.34 |
| **Alcohol drinkers, %** | 35.66 | 33.56 | 32.74 | 37.01 | 32.52 | 32.88 |
| **Tea drinker, %** | 64.96 | 66.92 | 68.45 | 64.3 | 67.47 | 68.3 |
| **Ginseng use, %** | 26.27 | 30.99 | 36.7 | 29.24 | 31.99 | 34.14 |
| **Ca Supplement use, %** | 3.07 | 4.36 | 5.91 | 4.02 | 4.67 | 5.11 |
| **Multivitamin use, %** | 3.92 | 6.92 | 10.04 | 6.00 | 7.58 | 8.32 |
| **Physically active, %** | 28.03 | 33.68 | 41.16 | 31.45 | 34.69 | 38.28 |
| **High school or up, %** | 14.39 | 22.37 | 29.02 | 19.14 | 23.91 | 25.07 |
| **Age (years), mean (SD)** [b] | 55.90(10.27) | 55.28(9.73) | 55.17(9.43) | 56.91(10.58) | 55.56(9.70) | 54.46(9.20) |
| **BMI(kg/m2), mean (SD)** [b] | 23.47(3.18) | 23.67(3.09) | 23.90(3.00) | 23.25(3.16) | 23.64(3.04) | 24.02(3.03) |
| **Daily nutrient intake adjusted for age and total energy, except for total energy** | | | | | | |
| **Total energy** [a] | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) | 1906.89(0.00) |
| **Saturated fat** | 8.16(0.03) | 9.74(0.03) | 11.85(0.03) | 9.59(0.04) | 9.92(0.03) | 10.88(0.03) |
| **Fiber** | 9.27(0.03) | 10.72(0.02) | 13.28(0.02) | 8.17(0.03) | 10.32(0.02) | 14.02(0.02) |
| **Phosphorus** | 956.75(1.17) | 1081.00(0.93) | 1271.73(0.87) | 953.79(1.56) | 1071.31(1.08) | 1270.89(1.11) |
| **Calcium** | 340.34(1.12) | 512.58(0.89) | 778.31(0.83) | 379.76(1.83) | 518.93(1.27) | 740.23(1.30) |
| **Magnesium** | 271.18(0.37) | 303.34(0.30) | 359.14(0.28) | 258.30(0.45) | 297.74(0.31) | 367.15(0.32) |
| **Retinol** | 120.06(1.17) | 154.78(0.93) | 198.50(0.87) | 142.50(1.41) | 156.14(0.98) | 183.74(1.00) |
| **Vitamin E** | 10.72(0.04) | 13.48(0.03) | 18.43(0.03) | 10.13(0.05) | 13.15(0.03) | 18.73(0.04) |
| **Folate** | 271.83(0.75) | 319.26(0.60) | 398.67(0.56) | 245.92(0.87) | 308.91(0.61) | 415.67(0.62) |
| **Sodium** | 250.29(0.92) | 345.02(0.73) | 489.36(0.68) | 271.89(1.28) | 345.24(0.89) | 470.94(0.91) |
| **Potassium** | 1464.92(3.41) | 1778.86(2.70) | 2289.70(2.53) | 1399.54(4.28) | 1739.67(2.97) | 2326.91(3.04) |
| **Zinc** | 11.54(0.01) | 12.23(0.01) | 13.40(0.01) | 11.38(0.01) | 12.13(0.01) | 13.50(0.01) |

[a] adjusted for age only. [b] SD, standard deviation.

**Table 2 Hazard Ratios (HRs) and 95% Confidence Intervals (95% CIs) for Total Mortality, and Mortality due to Cardiovascular Diseases and Cancer by Tertiles of Calcium and Magnesium among women in Shanghai**

| | Calcium intake (mg/day) | | | | | Magnesium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | P for trend | P for interaction | <251 | 251-<320 | ≥320 | P for trend | P for interaction |
| Person years | 349874.66 | 281646.47 | 175026.49 | | | 335378.89 | 271235.72 | 199933.00 | | |
| **Total Mortality** | | | | | | | | | | |
| Cases | 2019 | 1155 | 632 | | | 1992 | 1108 | 706 | | |
| Model 1 | 1.00 | 1.04(0.95,1.15) | 1.06(0.92,1.22) | 0.39 | | 1.00 | 1.04(0.94,1.16) | 1.09(0.94,1.27) | 0.27 | |
| Model 2 | 1.00 | 1.05(0.96,1.16) | 1.08(0.94,1.25) | 0.25 | 0.54 | 1.00 | 1.04(0.94,1.15) | 1.09(0.94,1.27) | 0.27 | 0.07 |
| [a] Ratio≤1.7 | 1.00 | 0.99(0.86,1.13) | 1.03(0.78,1.36) | 0.99 | | 1.00 | 1.14(1.00,1.30) | 1.24(1.02,1.51) | 0.02 | |
| [a] Ratio>1.7 | 1.00 | 1.03(0.85,1.24) | 1.06(0.81,1.39) | 0.68 | | 1.00 | 0.90(0.76,1.06) | 0.88(0.68,1.13) | 0.31 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | |
| Cases | 649 | 321 | 177 | | | 625 | 311 | 211 | | |
| Model 1 | 1.00 | 1.03(0.86,1.22) | 1.08(0.84,1.40) | 0.57 | | 1.00 | 1.11(0.92,1.34) | 1.35(1.03,1.77) | 0.04 | |
| Model 2 | 1.00 | 1.03(0.86,1.22) | 1.08(0.83,1.40) | 0.57 | 0.18 | 1.00 | 1.11(0.92,1.34) | 1.35(1.03,1.77) | 0.04 | 0.09 |
| [a] Ratio≤1.7 | 1.00 | 1.01(0.79,1.30) | 1.21(0.74,1.99) | 0.61 | | 1.00 | 1.17(0.93,1.48) | 1.53(1.08,2.16) | 0.02 | |
| [a] Ratio>1.7 | 1.00 | 0.95(0.67,1.35) | 1.07(0.64,1.79) | 0.69 | | 1.00 | 1.01(0.74,1.39) | 1.14(0.71,1.85) | 0.60 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | |
| Cases | 284 | 148 | 79 | | | 290 | 129 | 92 | | |
| Model 1 | 1.00 | 1.01(0.78,1.31) | 1.01(0.69,1.49) | 0.94 | | 1.00 | 0.96(0.73,1.28) | 1.19(0.79,1.78) | 0.46 | |
| Model 2 | 1.00 | 1.02(0.78,1.32) | 1.04(0.71,1.54) | 0.84 | 0.21 | 1.00 | 0.96(0.73,1.28) | 1.19(0.79,1.79) | 0.46 | 0.02 |
| [a] Ratio≤1.7 | 1.00 | 0.97(0.67,1.42) | 1.92(1.00,3.70) | 0.27 | | 1.00 | 1.01(0.70,1.46) | 1.69(1.02,2.80) | 0.07 | |
| [a] Ratio>1.7 | 1.00 | 0.86(0.53,1.40) | 0.85(0.41,1.76) | 0.68 | | 1.00 | 0.92(0.59,1.45) | 0.86(0.43,1.74) | 0.68 | |
| **Mortality due to Stroke** | | | | | | | | | | |
| Cases | 365 | 173 | 98 | | | 335 | 182 | 119 | | |
| Model 1 | 1.00 | 1.04(0.82,1.32) | 1.13(0.80,1.60) | 0.50 | | 1.00 | 1.25(0.97,1.61) | 1.50(1.03,2.16) | 0.03 | |
| Model 2 | 1.00 | 1.03(0.81,1.31) | 1.11(0.78,1.57) | 0.59 | 0.49 | 1.00 | 1.25(0.97,1.60) | 1.50(1.03,2.17) | 0.03 | 0.81 |
| [a] Ratio≤1.7 | 1.00 | 1.05(0.76,1.44) | 0.72(0.33,1.58) | 0.79 | | 1.00 | 1.30(0.95,1.77) | 1.40(0.87,2.23) | 0.12 | |
| [a] Ratio>1.7 | 1.00 | 1.07(0.65,1.77) | 1.35(0.66,2.77) | 0.34 | | 1.00 | 1.14(0.73,1.78) | 1.46(0.75,2.85) | 0.26 | |
| **Mortality due to all Cancers** | | | | | | | | | | |
| Cases | 789 | 556 | 271 | | | 756 | 537 | 323 | | |
| Model 1 | 1.00 | 1.09(0.95,1.26) | 0.90(0.72,1.12) | 0.51 | | 1.00 | 1.05(0.90,1.23) | 0.89(0.70,1.14) | 0.42 | |
| Model 2 | 1.00 | 1.10(0.95,1.27) | 0.92(0.74,1.15) | 0.68 | 0.24 | 1.00 | 1.05(0.90,1.23) | 0.89(0.70,1.14) | 0.42 | 0.78 |
| [a] Ratio≤1.7 | 1.00 | 1.03(0.85,1.26) | 0.82(0.54,1.25) | 0.73 | | 1.00 | 1.19(0.98,1.46) | 1.13(0.83,1.54) | 0.35 | |
| [a] Ratio>1.7 | 1.00 | 1.28(0.93,1.77) | 0.99(0.64,1.55) | 0.42 | | 1.00 | 0.85(0.66,1.10) | 0.61(0.41,0.92) | 0.02 | |
| **Mortality due to Lung cancer** | | | | | | | | | | |
| Cases | 171 | 109 | 50 | | | 156 | 109 | 65 | | |
| Model 1 | 1.00 | 1.00(0.73,1.37) | 0.76(0.47,1.24) | 0.34 | | 1.00 | 1.14(0.80,1.61) | 1.01(0.59,1.71) | 0.93 | |
| Model 2 | 1.00 | 1.02(0.74,1.40) | 0.81(0.50,1.32) | 0.47 | 0.87 | 1.00 | 1.15(0.81,1.62) | 1.01(0.60,1.72) | 0.92 | 0.95 |
| [a] Ratio≤1.7 | 1.00 | 1.13(0.73,1.76) | 1.78(0.82,3.87) | 0.22 | | 1.00 | 1.45(0.94,2.24) | 1.65(0.87,3.15) | 0.11 | |
| [a] Ratio>1.7 | 1.00 | 0.87(0.42,1.81) | 0.36(0.13,1.02) | 0.01 | | 1.00 | 0.64(0.36,1.13) | 0.30(0.11,0.77) | 0.01 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality due to Colorectal cancer** | | | | | | | | | | |
| Cases | 109 | 76 | 48 | | | 96 | 77 | 60 | | |
| Model 1 | 1.00 | 0.89(0.60,1.30) | 0.76(0.43,1.34) | 0.34 | | 1.00 | 1.19(0.78,1.82) | 1.32(0.70,2.51) | 0.39 | |
| Model 2 | 1.00 | 0.87(0.60,1.28) | 0.73(0.41,1.29) | 0.28 | 0.49 | 1.00 | 1.20(0.79,1.84) | 1.34(0.70,2.54) | 0.37 | 0.19 |
| [a] Ratio≤1.7 | 1.00 | 1.11(0.66,1.86) | 0.63(0.19,2.08) | 0.84 | | 1.00 | 1.92(1.11,3.33) | 2.20(0.96,5.04) | 0.05 | |
| [a] Ratio>1.7 | 1.00 | 0.50(0.23,1.10) | 0.32(0.11,0.94) | 0.05 | | 1.00 | 0.58(0.30,1.13) | 0.56(0.20,1.53) | 0.25 | |
| **Mortality due to Gastric cancer** | | | | | | | | | | |
| Cases | 108 | 68 | 32 | | | 114 | 58 | 36 | | |
| Model 1 | 1.00 | 1.15(0.77,1.72) | 1.05(0.57,1.92) | 0.80 | | 1.00 | 0.83(0.54,1.28) | 0.77(0.40,1.50) | 0.42 | |
| Model 2 | 1.00 | 1.17(0.78,1.75) | 1.09(0.59,2.03) | 0.69 | 0.23 | 1.00 | 0.83(0.54,1.28) | 0.77(0.40,1.50) | 0.42 | 0.33 |
| [a] Ratio≤1.7 | 1.00 | 0.75(0.42,1.35) | 1.34(0.47,3.77) | 0.81 | | 1.00 | 0.65(0.37,1.16) | 0.95(0.42,2.15) | 0.72 | |
| [a] Ratio>1.7 | 1.00 | 3.41(1.30,8.99) | 3.92(1.05,14.68) | 0.10 | | 1.00 | 1.10(0.54,2.23) | 0.63(0.20,2.01) | 0.49 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.
In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.
[a] Model 2 was used .

**Table 3 Hazard Ratios (HRS) and 95% Confidence Intervals (95% CIs) for Total Mortality, and Mortality due to Cardiovascular Diseases by Tertiles of Calcium and Magnesium among men in Shanghai**

| | Calcium intake (mg/day) | | | | | Magnesium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | ≥600 | p for trend | p for interaction | <251 | 251-<320 | ≥320 | p for trend | p for interaction |
| Person years | 77215.85 | 112600.73 | 147167.01 | | | 74633.02 | 109118.9 | 153231.68 | | |
| **Total Mortality** | | | | | | | | | | |
| Cases | 820 | 798 | 800 | | | 904 | 715 | 799 | | |
| Model 1 | 1.00 | 0.88(0.77,1.01) | 0.79(0.66,0.95) | 0.01 | | 1.00 | 0.80(0.70,0.93) | 0.87(0.70,1.07) | 0.23 | |
| Model 2 | 1.00 | 0.90(0.78,1.02) | 0.82(0.68,0.99) | 0.04 | 0.01 | 1.00 | 0.81(0.70,0.93) | 0.87(0.71,1.07) | 0.23 | 0.19 |
| [a]Ratio≤1.7 | 1.00 | 0.97(0.79,1.18) | 0.95(0.66,1.36) | 0.73 | | 1.00 | 0.98(0.79,1.21) | 1.23(0.90,1.69) | 0.19 | |
| [a]Ratio>1.7 | 1.00 | 0.70(0.56,0.89) | 0.59(0.44,0.80) | 0.00 | | 1.00 | 0.69(0.57,0.84) | 0.66(0.50,0.88) | 0.01 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | |
| Cases | 305 | 273 | 222 | | | 323 | 246 | 231 | | |
| Model 1 | 1.00 | 0.91(0.72,1.14) | 0.72(0.52,0.99) | 0.04 | | 1.00 | 0.87(0.68,1.11) | 0.83(0.58,1.20) | 0.33 | |
| Model 2 | 1.00 | 0.93(0.74,1.16) | 0.75(0.54,1.04) | 0.08 | 0.03 | 1.00 | 0.88(0.68,1.12) | 0.84(0.58,1.21) | 0.35 | 0.07 |
| [a]Ratio≤1.7 | 1.00 | 1.01(0.73,1.40) | 0.92(0.49,1.70) | 0.90 | | 1.00 | 1.17(0.83,1.66) | 1.02(0.60,1.73) | 0.91 | |
| [a]Ratio>1.7 | 1.00 | 0.91(0.59,1.40) | 0.73(0.42,1.29) | 0.19 | | 1.00 | 0.66(0.47,0.94) | 0.66(0.39,1.11) | 0.12 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | |
| Cases | 137 | 143 | 115 | | | 155 | 118 | 122 | | |
| Model 1 | 1.00 | 0.91(0.66,1.26) | 0.63(0.40,1.00) | 0.05 | | 1.00 | 0.69(0.49,0.98) | 0.64(0.38,1.08) | 0.10 | |
| Model 2 | 1.00 | 0.93(0.67,1.29) | 0.66(0.42,1.06) | 0.08 | 0.09 | 1.00 | 0.70(0.49,0.99) | 0.65(0.38,1.09) | 0.11 | 0.54 |
| [a]Ratio≤1.7 | 1.00 | 1.16(0.72,1.86) | 1.64(0.73,3.70) | 0.28 | | 1.00 | 1.01(0.61,1.68) | 0.91(0.42,1.96) | 0.81 | |
| [a]Ratio>1.7 | 1.00 | 0.88(0.47,1.65) | 0.48(0.21,1.09) | 0.02 | | 1.00 | 0.48(0.30,0.78) | 0.43(0.21,0.88) | 0.02 | |
| **Mortality due to Stroke** | | | | | | | | | | |
| Cases | 168 | 130 | 107 | | | 168 | 128 | 109 | | |
| Model 1 | 1.00 | 0.91(0.66,1.24) | 0.81(0.52,1.26) | 0.35 | | 1.00 | 1.08(0.77,1.53) | 1.06(0.63,1.76) | 0.84 | |
| Model 2 | 1.00 | 0.92(0.67,1.27) | 0.85(0.54,1.33) | 0.47 | 0.19 | 1.00 | 1.09(0.77,1.54) | 1.06(0.63,1.77) | 0.83 | 0.06 |
| [a]Ratio≤1.7 | 1.00 | 0.90(0.58,1.41) | 0.42(0.15,1.19) | 0.21 | | 1.00 | 1.32(0.82,2.12) | 1.08(0.52,2.24) | 0.78 | |
| [a]Ratio>1.7 | 1.00 | 0.99(0.54,1.80) | 1.20(0.54,2.65) | 0.52 | | 1.00 | 0.93(0.56,1.54) | 1.02(0.48,2.16) | 0.94 | |
| **Mortality due to all Cancers** | | | | | | | | | | |
| Cases | 320 | 337 | 394 | | | 335 | 316 | 400 | | |
| Model 1 | 1.00 | 0.86(0.70,1.05) | 0.79(0.60,1.04) | 0.10 | | 1.00 | 0.84(0.68,1.04) | 0.93(0.68,1.28) | 0.74 | |
| Model 2 | 1.00 | 0.87(0.71,1.06) | 0.81(0.61,1.07) | 0.14 | 0.23 | 1.00 | 0.84(0.68,1.05) | 0.93(0.68,1.29) | 0.75 | 0.97 |
| Ratio≤1.7 | 1.00 | 0.88(0.65,1.20) | 0.73(0.42,1.27) | 0.26 | | 1.00 | 0.93(0.66,1.30) | 1.31(0.80,2.13) | 0.26 | |
| Ratio>1.7 | 1.00 | 0.68(0.47,0.98) | 0.59(0.37,0.93) | 0.05 | | 1.00 | 0.80(0.60,1.06) | 0.74(0.49,1.14) | 0.19 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.

In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[a] Model 2 was used .

**Table 4 Hazard Ratios (HRS) and 95% Confidence Intervals (95% CIs) for Total Mortality, and Mortality due to Cardiovascular Diseases by Calcium and Magnesium intake among men in Shanghai**

| | Calcium intake (mg/day) | | | | | | Magnesium intake (mg/day) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <408 | 408-<600 | 600-<800 | ≥800 | p for trend | p for interaction | <251 | 251-<320 | 320-<420 | ≥420 | p for trend | p for interaction |
| Person years | 77215.85 | 112600.73 | 90733.06 | 56433.95 | | | 74633.02 | 109118.90 | 108337.41 | 44894.27 | | |
| **Total Mortality** | | | | | | | | | | | | |
| Cases | 820 | 798 | 486 | 314 | | | 904 | 715 | 564 | 235 | | |
| Model 1 | 1.00 | 0.93(0.81,1.06) | 0.79(0.66,0.95) | 1.03(0.80,1.31) | 0.50 | | 1.00 | 0.89(0.77,1.04) | 0.96(0.77,1.19) | 1.40(1.02,1.93) | 0.13 | |
| Model 2 | 1.00 | 0.95(0.83,1.09) | 0.83(0.69,1.00) | 1.12(0.87,1.44) | 0.97 | 0.01 | 1.00 | 0.89(0.77,1.04) | 0.96(0.78,1.20) | 1.41(1.02,1.93) | 0.13 | 0.19 |
| [a]Ratio≤1.7 | 1.00 | 0.96(0.79,1.17) | 0.98(0.68,1.40) | 0.70(0.29,1.68) | 0.63 | | 1.00 | 0.99(0.79,1.23) | 1.24(0.90,1.70) | 1.30(0.79,2.13) | 0.14 | |
| [a]Ratio>1.7 | 1.00 | 0.80(0.63,1.02) | 0.69(0.50,0.95) | 0.97(0.64,1.48) | 0.87 | | 1.00 | 0.84(0.68,1.03) | 0.83(0.61,1.13) | 1.39(0.89,2.17) | 0.48 | |
| **Mortality due to Cardiovascular Diseases** | | | | | | | | | | | | |
| Cases | 305 | 273 | 135 | 87 | | | 323 | 246 | 168 | 63 | | |
| Model 1 | 1.00 | 0.94(0.75,1.19) | 0.70(0.51,0.97) | 0.91(0.59,1.40) | 0.21 | | 1.00 | 0.93(0.72,1.20) | 0.88(0.61,1.28) | 1.20(0.69,2.08) | 0.95 | |
| Model 2 | 1.00 | 0.97(0.77,1.23) | 0.74(0.53,1.03) | 1.01(0.65,1.57) | 0.42 | 0.03 | 1.00 | 0.94(0.72,1.21) | 0.88(0.61,1.28) | 1.19(0.69,2.07) | 0.94 | 0.07 |
| [a]Ratio≤1.7 | 1.00 | 1.01(0.73,1.40) | 0.93(0.50,1.74) | 0.80(0.18,3.57) | 0.86 | | 1.00 | 1.19(0.84,1.70) | 1.02(0.60,1.74) | 1.18(0.51,2.74) | 0.89 | |
| [a]Ratio>1.7 | 1.00 | 1.05(0.67,1.65) | 0.86(0.48,1.56) | 1.31(0.61,2.82) | 0.70 | | 1.00 | 0.74(0.51,1.08) | 0.75(0.43,1.31) | 1.05(0.46,2.39) | 0.89 | |
| **Mortality due to Coronary Heart Disease** | | | | | | | | | | | | |
| Cases | 137 | 143 | 70 | 45 | | | 155 | 118 | 81 | 41 | | |
| Model 1 | 1.00 | 0.94(0.68,1.31) | 0.63(0.39,1.00) | 0.75(0.41,1.39) | 0.12 | | 1.00 | 0.79(0.54,1.14) | 0.72(0.42,1.23) | 1.18(0.54,2.56) | 0.88 | |
| Model 2 | 1.00 | 0.97(0.70,1.35) | 0.66(0.41,1.06) | 0.83(0.44,1.56) | 0.22 | 0.09 | 1.00 | 0.80(0.55,1.15) | 0.73(0.42,1.24) | 1.18(0.55,2.56) | 0.89 | 0.54 |
| [a]Ratio≤1.7 | 1.00 | 1.15(0.72,1.85) | 1.69(0.75,3.81) | 1.02(0.12,8.52) | 0.33 | | 1.00 | 1.05(0.62,1.77) | 0.92(0.43,2.00) | 1.20(0.37,3.92) | 0.99 | |
| [a]Ratio>1.7 | 1.00 | 0.94(0.49,1.82) | 0.52(0.22,1.20) | 0.63(0.21,1.86) | 0.14 | | 1.00 | 0.59(0.35,1.00) | 0.55(0.25,1.20) | 0.96(0.31,2.95) | 0.67 | |
| **Mortality due to Stroke** | | | | | | | | | | | | |
| Cases | 168 | 130 | 65 | 42 | | | 168 | 128 | 87 | 22 | | |
| Model 1 | 1.00 | 0.95(0.69,1.31) | 0.79(0.50,1.24) | 1.08(0.59,1.98) | 0.80 | | 1.00 | 1.09(0.76,1.56) | 1.06(0.63,1.78) | 1.08(0.48,2.41) | 0.89 | |
| Model 2 | 1.00 | 0.97(0.70,1.35) | 0.83(0.52,1.31) | 1.19(0.64,2.21) | 0.97 | 0.19 | 1.00 | 1.09(0.76,1.57) | 1.06(0.63,1.78) | 1.07(0.48,2.40) | 0.89 | 0.06 |
| [a]Ratio≤1.7 | 1.00 | 0.91(0.58,1.41) | 0.39(0.13,1.20) | 0.65(0.08,5.30) | 0.22 | | 1.00 | 1.31(0.81,2.13) | 1.08(0.52,2.24) | 1.04(0.30,3.57) | 0.92 | |
| [a]Ratio>1.7 | 1.00 | 1.25(0.66,2.34) | 1.57(0.68,3.63) | 2.97(1.00,8.87) | 0.04 | | 1.00 | 0.93(0.54,1.60) | 1.02(0.46,2.25) | 1.02(0.31,3.40) | 0.90 | |
| **Mortality due to all Cancers** | | | | | | | | | | | | |
| Cases | 320 | 337 | 236 | 158 | | | 335 | 316 | 273 | 127 | | |
| Model 1 | 1.00 | 0.90(0.73,1.10) | 0.80(0.60,1.05) | 0.95(0.66,1.38) | 0.55 | | 1.00 | 0.97(0.77,1.23) | 1.10(0.78,1.54) | 1.68(1.03,2.74) | 0.07 | |
| Model 2 | 1.00 | 0.91(0.74,1.12) | 0.82(0.62,1.08) | 1.00(0.68,1.46) | 0.72 | 0.23 | 1.00 | 0.97(0.77,1.23) | 1.10(0.78,1.54) | 1.68(1.03,2.74) | 0.06 | 0.97 |
| [a]Ratio≤1.7 | 1.00 | 0.88(0.65,1.19) | 0.75(0.43,1.31) | 0.51(0.15,1.79) | 0.21 | | 1.00 | 0.93(0.65,1.32) | 1.31(0.80,2.15) | 1.33(0.62,2.84) | 0.22 | |
| [a]Ratio>1.7 | 1.00 | 0.73(0.50,1.08) | 0.65(0.40,1.04) | 0.78(0.42,1.46) | 0.74 | | 1.00 | 1.03(0.74,1.42) | 1.04(0.65,1.66) | 1.91(0.97,3.76) | 0.18 | |

In Model 1, age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted.
In Model 2, Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.
[a] Model 2 was used .

**Table 5. Hazard Ratios (HRS)[a] and 95% Confidence Intervals (95% CIs) for Total Mortality by tertiles of calcium and magnesium intake among women and men stratified by the median intake of magnesium and calcium, respectively.**

| | | Calcium intake (mg/day) | | | | |
|---|---|---|---|---|---|---|
| | | **<480** | **480-<600** | **≥600** | **p for trend** | **p for interaction** |
| SWHS | All subjects | 1.00 | 1.05(0.96,1.16) | 1.08(0.94,1.25) | 0.25 | 0.42 |
| | [b]Mg≤284.3 | 1.00 | 1.06(0.95,1.19) | 1.19(0.93,1.52) | 0.15 | |
| | [b]Mg>284.3 | 1.00 | 0.84(0.69,1.03) | 0.82(0.64,1.05) | 0.19 | |
| SMHS | All subjects | 1.00 | 0.90(0.78,1.02) | 0.82(0.68,0.99) | 0.04 | 0.11 |
| | [b]Mg≤284.3 | 1.00 | 0.97(0.82,1.14) | 0.91(0.68,1.22) | 0.54 | |
| | [b]Mg>284.3 | 1.00 | 0.88(0.67,1.16) | 0.75(0.54,1.03) | 0.03 | |
| | | **Magnesium intake (mg/day)** | | | | |
| | | **<251** | **251-<320** | **≥320** | **p for trend** | **p for interaction** |
| SWHS | All subjects | 1.00 | 1.04(0.94,1.15) | 1.09(0.94,1.27) | 0.27 | 0.42 |
| | [c]Ca≤491 | 1.00 | 1.12(0.99,1.26) | 1.31(1.05,1.64) | 0.01 | |
| | [c]Ca>491 | 1.00 | 0.79(0.64,0.98) | 0.70(0.52,0.95) | 0.03 | |
| SMHS | All subjects | 1.00 | 0.81(0.70,0.93) | 0.87(0.71,1.07) | 0.23 | 0.11 |
| | [c]Ca≤491 | 1.00 | 1.00(0.82,1.21) | 1.59(1.15,2.20) | 0.06 | |
| | [c]Ca>491 | 1.00 | 0.70(0.55,0.88) | 0.57(0.42,0.79) | 0.00 | |

[a] Model 2 was used. age at entry, sex, body mass index (BMI), education, marriage status, smoking status, tea drinking, use of ginseng, alcohol drinking, use of Ca supplement, use of multivitamin, regular physical activity and intakes of total energy, saturated fatty acid, phosphorus, fiber, retinol, vitamin E, folic acid, sodium, potassium, and zinc were adjusted. Ca and Mg were further adjusted to assess whether the association of Mg or Ca was independent of Ca or Mg, respectively.

[b] Mg= magnesium intake

[c] Ca= calcium intake

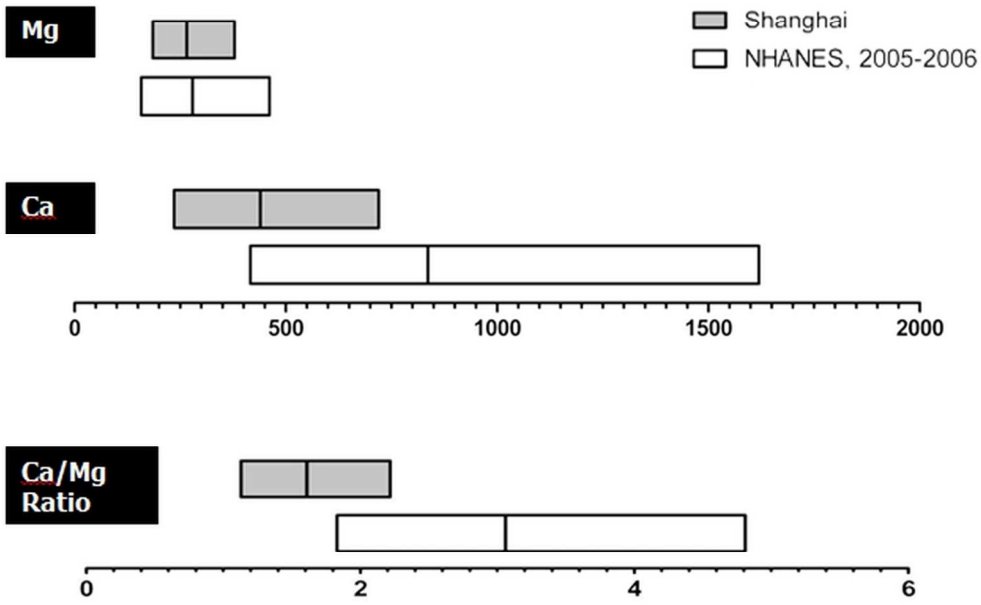



**Figure 1.** Comparison of intake levels of Ca (mg/day), Mg (mg/day) and Ca/Mg ratio in US and Shanghai, China

106x90mm (300 x 300 DPI)